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(54) Title: METHOD AND DEVICE FOR IMPLANTATION OF LARGE DIAMETER OBJECTS IN BOVINES

(57) Abstract

A method and device for implanting large diameter objects subcutaneously or into the peritoneal cavity of bovines employs a beveled, puncturing, but substantially non-incising trocar.

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METHOD AND DEVICE FOR IMPLANTATION OF LARGE DIAMETER OBJECTS IN BOVINES

Field of the Invention

The invention relates to method and device for implantation of large diameter devices or capsules in bovines. In one aspect, the invention relates to a method of implantation which is effective and from which the bovine readily heals. In another aspect, the invention relates to a device specifically adapted for intraperitoneal implantation in bovines which can be used in such a method.

Setting of the Invention

In the field of raising cattle for dairy products and meat, it is sometimes desirable for various reasons to implant a large diameter object subcutaneously or in the intraperitoneal cavity of the bovines. For example, in preparing finishing beef cattle for slaughter, it may be desired to insert a prolonged release device or capsule or pellet into the intraperitoneal cavity to enhance average daily gain, body weight, carcass weight, dressing percentage and the like. As another example, in enhancing milk production in dairy cattle, it may be desirable to implant such devices or capsules or pellets subcutaneously. See Appendixes A and B attached hereto and incorporated herein by reference. It may also be desirable to implant large diameter devices such as temperature monitors and other electronic instrumentation, animal identification transponders, and the like. Many other large diameter devices will occur to those skilled in the art.

Such devices or capsules or pellets in order to provide a suitably prolonged release and to be readily visible after the slaughter of the animal may be of substantial size. However, feedlot operators and technicians and cattle and dairy farmers are reluctant to undertake such treatment with large diameter objects, although advantageous and economically beneficial, unless it can be accomplished readily, without significant injury to the bovine, requires minimal care, and suitably heals. Thus, implantation of large diameter objects presents a significant problem to animal husbandry and also to the providers of treatments and devices for cattle.

The prior art has dealt with devices for injection of liquids into the peritoneal cavity and with trocars for relieving bloating of the rumen. The rumen is the first division of the stomach of a ruminant animal, distended into the peritoneal cavity, in which food is partly digested before being regurgitated for further chewing.

The prior art has also dealt with devices for subcutaneous implantation of pellets. The pellets are generally of relatively small diameter and the implanters generally have hide-incising tips which, if they were made larger and came into contact with underlying tissues, would cause relatively extensive bleeding and damage. Moreover, coring of the hide and underlying flesh could result, facilitating peritonitis if such materials were discharged into the peritoneal cavity, and generally impeding healing.

Summary of the Invention

In accordance with the invention, a method is provided for implanting large diameter objects in the intraperitoneal cavity of bovines which can be

accomplished readily, without significant injury to the bovine, requires minimal care after implantation, and suitably heals.

The method comprises providing a generally cylindrical large diameter object with an outside diameter in the range of about 8 to about 15 millimeters (mm). An incision is made in the hide of the left paralumbar fossa of the bovine, the incision having an orientation and length and depth such that gaping of the resulting wound substantially does not occur after inserting an object therethrough. A generally cylindrical tube having an external diameter of less than about 25mm for passing through the opening and having an internal diameter for passing the large diameter objects therethrough and having a non-hide-incising tip effective for penetrating underlying tissues and for puncturing the peritoneum and a length for extending through the incision, the underlying tissues and into the peritoneal cavity, is inserted into the incision, and is caused to puncture and penetrate the peritoneum, and the large diameter objects are inserted therethrough. The tube is removed and the incision in the hide closes.

In accordance with a further aspect of the invention, there is provided a device for the subcutaneous or intraperitoneal implantation of large diameter substantially size-invariant objects into a bovine. The device comprises a plastic tube having an outside diameter of less than about 25mm and an inside diameter effective for passing therethrough objects having an outside diameter in the range of about 8 to about 15 mm. A first end of the tube is beveled and has a non-hide-incising tip effective for penetrating tissues underlying an incision in the hide and for puncturing the peritoneum. Adjacent the first end is means for releasably retaining large diameter objects in the tube while the tube is

inserted into the incision in the bovine's hide. Adjacent the second end is a slidable seal which can be urged to deliver the large diameter objects within the tube past the releasing means and out of the first end of the tube.

In accordance with another aspect of the invention there is provided a disposable administration package or article of manufacture for intraperitoneal administration of a beneficial agent to a bovine. The article comprises a disposable plastic tube having a non-hide-incising tip at a first end, the tip being effective for penetrating bovine tissues underlying an incision in the hide and being effective for penetrating the intraperitoneal cavity of the bovine. A plastic sheath sterilely encloses a first portion of the tube adjacent a first end, the first portion having a length effective for extending from left paralumbar fossa of a bovine into the intraperitoneal cavity. Retaining means is provided adjacent the first end for releasably retaining objects within the tube after the sheath is removed. The tube encloses one or more osmotically-driven pumps having an outside diameter of about 8 to about 15mm for delivery of a beneficial agent. A seal adjacent the second end of the tube completes sterile or low bioburden enclosure of contents of the tube.

The invention will be further understood and appreciated from the following detailed description and the drawings in which:

Figure 1 is a line drawing of the hind portion of a bovine showing a typical arrangement of left paralumbar fossa, an adjacent portion of the intraperitoneal cavity, and the rumen.

Figure 2 is a modified Figure 1 showing an incision made in the hide of the bovine and a device in accordance with the invention inserted into the

opening and through the peritoneum into a portion of the peritoneal cavity.

Figure 3 is a schematic illustration of a device for implanting large diameter objects mounted in a gun for administering the implants, all in accordance with the invention.

Figure 4 illustrates the exterior appearance of a device in accordance with the invention.

Figure 4A is a longitudinal section along the line 4A-4A in Figure 4.

Figure 5 is a detail drawing showing the appearance of the obverse side of the tip of the device of Figure 4.

Figure 6 is a longitudinal section of the portion designated 6 in Figure 3.

Figure 7 is a detail drawing illustrating a longitudinal section through the tip of the invented trocar.

Figure 8 is a detail drawing of the portion designated 8 in Figure 4.

Figure 9 illustrates removal of the sheath from the combined trocar and gun of Figure 3.

Figure 10 illustrates a longitudinal section through a seal adjacent the second end of an embodiment of the invented trocar.

Figure 11 illustrates the exterior appearance of cap 102b.

Figure 12 illustrates an axial longitudinal section along the line 12-12 in Figure 11.

Figure 13 illustrates in detail the region identified as 13 in Figure 12.

Figure 14 illustrates a package in accordance with the invention.

Figure 15 illustrates a sealed package comprising a plurality of sterile packages in accordance with Figure 3.

The invention will now be described in detail showing preferred embodiments of the invention, but

is not limited thereto, but by the claims appended hereto interpreted in accordance with law.

Detailed Description of the Invention

In accordance with the invention, a method is provided for implanting large diameter objects in the intraperitoneal cavity of bovines which can be accomplished readily, without significant injury to the bovine, requires minimal care after implantation, and readily heals.

The method comprises providing a generally cylindrical size-invariant large diameter object with an outside diameter in the range of about 8 to about 15mm. The objects can be, for example, capsules, pellets, mechanical or osmotic pumps for delivering beneficial agents, electronic identification devices and monitors, and the like. As used herein, size-invariant refers to an object whose diameter does not significantly alter during implantation, for example, by crushing or otherwise. In a preferred embodiment, the objects are osmotic pumps for the delivering of a beneficial agent such as described in Appendix A incorporated herein by reference.

The minimum outside diameter of the large diameter objects in accordance with the invention is about 8mm since it has been found that such devices can be made effective for delivering a beneficial agent over a prolonged length of time, and can be readily identified at the time of slaughter. The maximum outside diameter in accordance with the invention is about 15mm since larger diameter objects require an incision in the hide of the animal greater than about 20 to 25 mm in length and it has been determined that when the incision is less than this range that substantial sealing of the wound occurs rapidly, often within 15 minutes or less of implantation, so that mechanical force is required to reopen the incision, and very low incidence of

injection site responses is observed. Further the peritoneal wound also effectively heals and when low bioload or sterility of the device is maintained little or no peritonitis other than localized non-septic peritonitis has been observed. See Examples 1 and 2 below.

In accordance with an aspect of the invention, an incision is made preferably vertically, in the hide of the left paralumbar fossa of the bovine, the incision having a length of less than about 20 to 25mm such that gaping of the resulting wound does not occur after inserting an object therethrough and the wound readily seals. Preferably the incision is vertical relative to the ground, only in the hide, and substantially not in the underlying muscle layers which are more highly vascularized, thus minimizing bleeding. Controlled incision is also preferable because to the extent the underlying muscle tissues are incised, gaping of the wound is more likely to occur at shorter lengths of incision due to symmetrical destruction of the underlying tissues. The incision can be made by means known in the art such as scalpel, laser, and the like.

In accordance with the invention, large diameter substantially size-invariant objects are provided for intraperitoneal implantation. Such objects can be, for example, pellets or capsules of bovine somatotropin, of estrogen, or other metabolic regulators or drugs, or electronic devices and monitors. For example, the objects can be appropriately sized bovine somatotropin pellets as disclosed in U.S. 5,091,185. Alternatively and preferably, such objects can be devices for delivering bovine somatotropin and/or estrogen at a pulsatile or substantially constant rate such as described in Appendixes A and B attached hereto and incorporated herein by reference. Most preferably the objects are osmotic pumps such as are described

in Appendix A attached hereto and incorporated herein by reference.

In accordance with a preferred embodiment of the invention, a disposable plastic generally cylindrical tube having an external diameter of less than about 25mm, for example 20mm, for passing through the incision and having an internal diameter for passing the large diameter objects therethrough and having a substantially non-hide-incising tip effective for penetrating underlying tissues after the incision has been made and for puncturing the peritoneum and having a length for extending through the incision, the underlying tissues and into the peritoneal cavity, is inserted into the incision, is caused to penetrate the underlying tissues and to puncture and penetrate the peritoneum, and the large diameter objects are inserted therethrough. Preferably the length inserted into the bovine is sterile prior to use.

As used herein, plastic according to its general technical usage refers to a high polymer, usually synthetic, optionally combined with other ingredients such as curatives, fillers, reinforcing agents, colorants, plasticizers, and the like, which can be formed or molded under heat or pressure in its raw state and machined to high dimensional accuracy, trimmed and finished in its hardened state.

The puncturing non-incising tip is beveled or slanted to facilitate passage through underlying tissues, but is substantially non-incising to reduce cutting or coring or both of the underlying tissues. Use of a beveled, mostly non-incising tip to pass through the muscle layers results in tearing, rather than incision, of the muscles; and damage to vascular structure and bleeding is reduced and healing facilitated because of quicker clotting and other factors. Preferably the bevel is less than 35° since 40° and 45° bevels cannot efficiently be urged

through underlying tissues. 30° is much better than 35°, while 25° is only marginally better than 30°. To minimize length of the trocar it is preferred that the bevel be in the range of about 25° to about 35° relative to the horizontal axis.

The peritoneum is the serous membrane lining of the abdominal walls (parietal peritoneum) and investing the viscera (visceral peritoneum). The parietal peritoneum is the membrane which lines the abdominal and pelvic walls and the undersurface of the diaphragm. The visceral peritoneum is the membrane reflected at various places over the viscera, forming a complete covering for the stomach, spleen, liver, ascending portion of the duodenum, jejunum, ileum, transverse colon, sigmoid flexure, upper end of the rectum, uterus, and ovaries; it also partially covers the descending and transverse portions of the duodenum, the cecum, ascending and descending colon, the middle part of the rectum, the posterior wall of the bladder, and the upper portion of the vagina. The peritoneum serves to hold the viscera in position by folds, some of which form the mesenteries, which connect portions of the intestine with the posterior abdominal wall; others form the omenta, folds attached to the stomach, and still others, the ligaments of the liver, spleen, stomach, kidneys, bladder, and uterus. The space between the parietal and visceral peritoneums is the peritoneal cavity, which consists of the pelvic peritoneal cavity below and general peritoneal cavity above. The general peritoneal cavity communicates by the foramen of Winslow with the cavity of the great omentum, which is also known as the lesser peritoneal cavity. As used herein, intraperitoneal cavity includes any of the pelvic peritoneal cavity, the general peritoneal cavity, and the lesser peritoneal cavity. More preferably, the implant is inserted into the lesser peritoneal cavity.

It has been discovered that access to the peritoneal cavity in bovines is best gained through the left paralumbar fossa in bovines which have been fasting or feed-restricted as discussed below. Initially, it was thought that insertion through the right paralumbar fossa would be the preferred side, as the rumen is positioned adjacent the left paralumbar fossa, and it was desired to avoid the possibility of damage to the rumen. However, the kidneys and associated kidney fat are asymmetrically distributed in the bovine toward the right side of the body and interfere with access to the peritoneal cavity on that side and further require a longer tube for implantation to assure that the implants are discharged into the intraperitoneal cavity and not into kidney fat or kidney where ineffective release or damage to the animal would occur. For this reason access to the intraperitoneal cavity in accordance with the invented method is accomplished through the left paralumbar fossa.

Referring to Figure 1, the left paralumbar fossa is a generally triangular area 42 of about 6-8 inches diameter on bovine 40 between the hip bone 44 and the last rib and below the loin area on the left side. Tissue and hide depth here is typically about 0.5 to 2.0", hence tubes used for intraperitoneal implantation can be generally on the order of 1 to 5 inches or longer. The insertion depth of the tube needs to be greater than the actual thickness of the paralumbar region due to the potential for stretching of the peritoneal lining. As indicated above, the only internal organ presenting a risk of injury via the left paralumbar fossa is the rumen 46, provided the trocar is not pointed upward toward the kidney.

Damage to the rumen can be eliminated or reduced by applying the invented method to animals whose rumen is not too much distended into the target peritoneal cavity, for example, to fasting or feed-

restricted animals. Preferably animals treated in accordance with the invented method have been fasting or feed restricted (reduced feed or water-only) for 6 to 24 hours, most preferably about 10 to 18 hours prior to administration since it has been observed that the rumen is typically flaccid or at least not typically distended into the implantation area at this time facilitating avoidance of injury.

After implantation, the specified incision in the hide (See reference numeral 46 is Figure 1), which is preferably vertical to facilitate closure and to prevent pooling of blood and fluids during closure, is often already undergoing sealing and closure in 15 minutes to 1 hour so that force would have to be applied to reopen the incision. Investigation of the length of incision has shown that so long as the length is less than about 25mm, more preferably, less than about 20mm, this rapid sealing phenomenon is observed. Likewise, examination of bovines following slaughter has shown that they are overwhelmingly free of signs of peritonitis other than localized non-septic peritonitis.

The invention can be further illustrated by reference to the Figures, particularly Figures 1 and 2, wherein reference numeral 40 indicates the left paralumbar region of a bovine 42, reference numeral 44 indicates the targeted portion of the peritoneal cavity, 46 indicates the adjacent rumen, and 48 illustrates a vertical incision in the left paralumbar fossa. Referring now to Figure 2, Figure 2 further shows administration gun 140 having device 102 mounted therein inserted into the targeted peritoneal cavity 44.

Thus, in accordance with the invention, a method has been provided for implanting large diameter objects in the intraperitoneal cavity of bovines which can be accomplished readily, without

significant injury to the bovine, requires minimal care after implantation, and rapidly heals.

In accordance with another aspect of the invention, there is provided a device for the intraperitoneal implantation of large diameter size-invariant objects into a bovine.

The device preferably comprises a plastic tube having an outside diameter of less than about 25mm, preferably less than about 20mm, and an inside diameter for passing therethrough large diameter size-invariant objects having an outside diameter in the range of about 8 to about 15 mm. In a first portion of its length which can be sized to extend from hide to intraperitoneal cavity in a bovine, the outer surface of the first portion is preferably sterile prior to use. A first end of the tube adjacent the first portion is beveled and has a puncturing but substantially non-hide-incising tip having a hardness and stiffness effective for puncturing the peritoneum. Adjacent the first end is means for releasably retaining the large diameter objects in the tube while the tube is inserted into an incision in the bovine's hide. Adjacent the second end is a slidable seal which can be urged to deliver the large diameter objects within the tube past the releasing means and out of the first end.

Referring now to Figure 3, Figure 3 illustrates administration gun 140 having package 102 mounted therein. Gun 140 has push rod 142 which can be used to deliver implants 128 as hereinafter described.

Referring now to Figure 4, package 102 comprises trocar 102a and its contents hereinafter described and sheath 102b. Reference numeral 102a indicates a generally cylindrical plastic tube of unitary construction having an outside diameter of less than about 25mm and an inside diameter capable of receiving generally cylindrical size-invariant

objects having an outside diameter in the range of about 8mm to about 15mm.

As illustrated, the generally cylindrical plastic tube 102a may overall slightly taper distally, as illustrated, from right to left, sufficient to facilitate molding and mold-release of the device. The sidewall thickness of the device can also narrow distally as best illustrated in Figure 13. The device is of a moldable or machinable plastic, preferably a moldable plastic having a hardness such that a tip 104 can be molded or machined tip effective for puncturing the peritoneal membrane but is otherwise substantially non-incising. Alternatively, a puncturing tip may be attached to the tube after construction or during molding. The generally cylindrical tube can be made of any non-toxic plastic which has appropriate strength, moldability, stiffness and, optionally, low moisture transmission rate. Thus the generally cylindrical tube can be polycarbonate, polyvinylchloride, acrylonitrile-butadiene-styrene (ABS), and the like. ABS is preferred because of its strength, moldability, stiffness and low moisture transmission rate, for example, Lustran® ABS available from Monsanto Company, St. Louis, MO. The trocar can have a slight taper on both the interior and exterior sidewall to facilitate molding. Preferably, however, there is no taper of the interior diameter where seal 134 (See Figure 4A) is seated adjacent the preferably chamfered second end as illustrated by reference numeral 118a; nor preferably is there taper of the exterior diameter in portion 116a, adjacent shoulder 120, where the sheath seals to the tube.

Device 102 comprises a first end 106 and a second end 108. First end 106 has a tip 104 which can be formed by double-beveling the tip of the tube, as illustrated. Generally, as discussed above, the primary bevel 110 is in the range of about 20 to 35

degrees, while the secondary bevel 112 (See Figure 8) is in the range of 30 to 40 degrees measured as the angle between the bevel and a plane perpendicular to the longitudinal axis of the trocar, for example 34 degrees. Preferably, as illustrated, the bevels are selected to minimize the length of device 102 while providing a suitable puncturing tip. The inside surface or heel of tube 102, as illustrated at 115 in Figure 6, can be rounded slightly to minimize roughness and the tendency to scrape and carry flesh, hair, and the like as device 102 is inserted into the flesh of an animal. The lower surface of the tip, as best illustrated by reference numeral 150 in Figure 7, can be angled, for example, at about 5° relative to a longitudinal axis, to reduce thickness of the puncturing tip.

As illustrated, device 102 consists of first and second body portions 116 and 118 respectively, having substantially the same or slightly distally tapering inside diameters and different outside diameters forming a shoulder 120 therebetween. Shoulder 120 can be used to receive and seat the sheath, discussed below, and also to gauge or limit insertion of device 102 into a bovine after the sheath is removed. Alternatively, the outside diameters can be the same. The length of the first portion from shoulder 120 to tip 104 is preferably sufficient to extend from the hide to the peritoneum of a bovine at the left paralumbar fossa. Thus, this length can be on the order of 1 to 5 inches. 4 inches has been found to be effective for puncturing the peritoneum even with a relatively inefficient tip. With a more efficient tip a lesser length of the first portion will be advantageous. Longer lengths can also be used.

As illustrated, a closed cap or sheath 102b having a coaxial tubiform spacer 124 molded in the tip thereof and having a generally cylindrical wall

126 is inserted on the first portion 116 maintaining the outer surface sterile before use. Spacer 124 has a length for ensuring that implants 128 do not rest on protuberance 130 while cap 102b is on device 102. As illustrated, molded sealing rings or annular ridges 127 of wall 126 (See Figures 12 and 13) rest against shoulder 120. Cap 102b is preferably constructed of an elastomeric material such that the annular rings will snuggly but removably engage portion 116a of trocar 102a. Sheath 102b can be molded of any plastic which has suitable moldability and pliability to allow for maintaining a sterility and/or moisture seal when installed on device 102. Optionally, the plastic can have a low moisture transmission rate. A preferred plastic is a polypropylene, for example, one having the characteristics of Himont PD626 available from Himont, Wilmington, DE. The length of the sheath is determined by the length of the device 102 which will be inserted into contact with bovine tissues, i.e., the combined length of 116a and 116b. The sheath can be slightly tapered so as to facilitate mold-release and to avoid a vacuum when sheath 102b is removed from device 102.

According to the invention, means is provided adjacent the tip for releasably retaining implants 128 within device 102 when the cap is removed and device 102 is held vertically. Many suitable means will occur to those skilled in the art. Preferably the means is of a type which can be molded and is made of the same material as device 102 since this simplifies manufacture. In the illustrated embodiment, the means comprises a bump or convex protrusion 130 (See Figures 4, 6, 7, and 8) which is molded on the interior sidewall of portion 116b on a flexible strip 131 (See Figures 5 and 8) bounded by longitudinal slits 132 passing through the sidewall. When cap 102b (See Figure 9) is removed and implant

128 is urged, as hereinafter described, by push rod 142 toward tip 102, the pressure exerted by the implant 128 on protuberance 130 will cause strip 133 (See Figure 6) to bow outwardly permitting passage of implants 128. When cap 102b is in place, for example during shipping and handling, spacer 124 maintains the implants away from protuberance 130. Thus cap 102b, spacer 124, and the retaining means cooperate to provide an effective, moldable device.

In the illustrated embodiment of Figure 3, second portion 118, together with first portion 116, and cap 102b constitute device 102. The combined length of device 102 is determined by the length of portion 116 which will traverse the bovine from hide to peritoneal cavity and by the total length required for mounting in gun 140 and for enclosing a desired number of implants 128. Preferably, the number of implants 128 is a number that will be implanted in one bovine during one administration. This number may be 1, 2, 3, or more.

Adjacent the second end of device 102 is a seal 134 for sealing (best seen in Figures 4A and 10) and, in cooperation with cap 102b, for maintaining sterility of the interior of device 102. After insertion of seal 134 the tube 102 can be heat treated adjacent the second end to provide a stop ridge (not illustrated) holding seal 134 within tube 102. Preferably the seal is a molded plug comprising bumper 136, first and second side wall engaging members 138 and body 140. Preferably all parts are generally cylindrical but may be of different shapes effective for their respective purposes as will be apparent to those skilled in the art. The seal 134 preferably includes a generally cylindrical, preferably slightly frustoconical well 142 optionally radiused at its proximal end and narrowing distally therein, for engaging and being engaged by rod 142 to urge implants 128 past protuberance 130 and out of

the first end 106 of device 102. The seal will engage rod 142 (See Figure 5) which will preferably have a length and/or range of travel such that seal 134 cannot be expelled from the first end of device 102 during use. Preferably the point of contact between the rod and the piston is past the center point of the piston to limit the tendency for sealing edges to be deviated as the seal is advanced. Bumper or spacer 136 has a diameter less than the smallest diameter adjacent protrusion 130 and a length sufficient to ensure that implants 128 can be urged beyond a point of possible engagement with protrusion 130.

Seal 134 can preferably be molded from any suitable plastic or rubber such as a thermoplastic elastomer having suitable sealing and deforming characteristics, for example, the ability to produce a sterile and optionally a moisture seal along a device having a slight taper. Particularly preferred is Santoprene® 271-55 brand thermoplastic elastomer, available from Monsanto Company St. Louis, MO, which is deformable but noncompressable under conditions of use, and has the ability to produce both sterility and moisture seals and to compensate for sidewall irregularities and taper. Other seals, such as seals using O-rings or fabricated of other materials can also be used.

Referring now to Figures 4, 5, 6, 7 and 8, these Figures illustrate the positioning of strip 133, bounded by slits 131, and having protuberance 130 thereon, in a preferred embodiment of the device. As illustrated, this type of retaining means, which can be included in a mold for device 102, is positioned on the side of tube 102 having the greatest length. In this way, it is insured that slits 131 are adjacent to but do not open onto tip 104 where the openings could snag tissue and carry hair and other contaminants into the bovine. As best

illustrated in Figures 4, 6 and 8, protuberance 130 is preferably positioned opposite or counter to the shortest length of tube 102. In this way implants 128 are maintained in the sterile interior environment of tube 102 until use, and the overall length of 102 can be kept to a minimum. Other retaining means are known to those skilled in the art and may be used such as, for example, those disclosed in U. S. Patents 2,587,364 incorporated herein by reference, O-rings, and the like.

Referring again to Figures 3 and 9, these Figures illustrate a device 102 mounted in a gun 140 having a push rod 142. Such devices are well-known in general and it suffices to the person skilled in the art to point out that gun 140, adapted for device 102, should firmly grasp device 102 in such a way that cap 102b can be removed (See Figure 9) after insertion in the gun and to minimize wobble during implantation. Further, push rod 142 should have a length and/or range of travel such that seal 134 of device 102 cannot be expelled from first end 106.

Referring now to Figure 14, this Figure illustrates a package 102 in accordance with the invention comprising body 102a and closed sheath 102b and containing between spacer 124 and seal 134 two implants 128, such as, for example, bovine somatotropin implants described in Appendix A attached hereto and incorporated herein by reference. Conditions of manufacture and loading are such that implants 128, and the interior and exterior surfaces of device 102 are preferably of low bioload and more preferably sterile. It is also envisioned that device 102 can be constructed of materials which are substantially impermeable to water since, as described in Appendix A, the osmotic implants may include salt tablets whose exposure to moisture prior to use would result in variable performance at startup. Alternatively, one or a plurality of

devices 102 could be packaged in a water- impermeable material, such as foil 160, as illustrated in Figure 15.

Example 1

This example illustrates the significance of the incision in the hide being vertical and approximately 25, or 20mm, in length or less.

Cattle were intraperitoneally implanted using a 12.6mm outside diameter metal trocar inserted through an incision approximately 18-20mm in length and vertical relative to the ground. On occasion animals have been checked after an incision was made. The time lapse would vary from approximately 10-60 minutes. In all instances the incision had completely closed and required that physical force be utilized to re-open the initial incision for trocar insertion. During implantations an effort is made to keep incisions less than approximately 25mm in length and not to cut the muscle layers beneath. It has been observed that when incisions are greater than 25mm or if the muscle layers are cut with a scalpel that the incision has the propensity to gap open after the trocar has been removed.

Histological examination has been performed on the scar left after implantation at 21 and 40 days post implantation. At 21 days, the lesion resembles a capital "I". The transverse upper portion of the "I" lies directly beneath the epidermis and extends laterally in each direction for approximately 1mm. It consists of a dense wide band of highly cellular collagen, primarily fibroblasts. Occasional small pockets of inflammatory cells such as polymorphs and lymphocytes do not exceed a dozen or so cells. The inflammatory portion of the reaction period is well passed. The overlying epidermis is normal. The vertical portion of the "I" passes through the

subcutaneous musculature in the form of nearly mature collagen containing occasional penetrating new vessels. Beneath the musculature the "I" extends outward as a web of similarly almost mature collagen.

At 40 days the epidermis is normal and intact. The only evident lesion consists of a narrow finger of mature collagen extending from the subcutis through musculature.

The epidermis was intact and normal in all animals indicating the sites would be difficult to detect grossly. Collagenous scar tissues was normal and had very limited numbers of inflammatory cells. The collagenous tissue still distinctly contained fibroblasts at 21 days and lesser numbers at 40 days indicating that the final shrinkage, as seen in mature scar tissue, was in progress.

Example 2

This example illustrates that use of a low-bioburden device having an outside diameter of 25, or 20mm, or less, does not result significantly in peritonitis in bovines, other than in localized non-septic peritonitis.

A series of trials were conducted with stainless steel trocars for insertion of non-sterile, low-bioburden 5, 8 and 10 mm osmotic implants dispensing solutions of bovine somatotropin (bST).

In the first set of trials, 5mm osmotic implants dispensing bST at a rate of about 2 to 3 mg/d were implanted into the peritoneal cavity of 902 cattle. The trocar had an outside diameter of 7.1mm and a maximum insertion length of about 9 cm. In the case of 672 of these animals, the animals received a second intraperitoneal implantation 42 days prior to slaughter; while the remaining 230 cattle received only one intraperitoneal implantation 42 days prior to slaughter. At slaughter there was a 3-5% incidence of localized non-septic peritonitis

observed by the USDA Inspector-in-Charge; however implants were difficult to recover, in part due to their small size (5mm) and to their lack of color (clear). No septic peritonitis was observed.

In the second set of trials 953 cattle were implanted intraperitoneally with non-sterile low-bioburden 8mm, blue osmotic implants dispensing bST at a rate of about 6 to 9 mg/d. The trocar had an outside diameter of about 9.6 mm and a maximum insertion length of about 10 cm. The cattle were slaughtered about 90 days post-implantation. These implants were easier to recover and the incidence of localized non-septic peritonitis was comparable to that observed with the 5 mm osmotic implants. No septic peritonitis was observed.

In a third set of trials 1153 cattle were implanted with non-sterile 10mm, blue, osmotic implants dispensing bST at a rate of about 6 to 10 mg/d. The trocar used for implantation had an outside diameter of about 12.6 mm and a maximum insertion length of 10 cm. The cattle were slaughtered 120 to 140 days post-implantation. In two of these trials, each with approximately 288 implanted cattle, the non-sterile implants had a relatively high bioburden and the incidence of adhesions between the parietal peritoneum and the visceral peritoneum and the incidence of localized peritonitis with a more severe appearance affecting larger areas of the peritoneum cavity was observed to have increased. The increased bioburden indicates the desirability of sterile or at least low bioburden implants to avoid higher levels of adhesions and increased severity of localized peritonitis. In subsequent trials with low bioburden 10 mm implants it has been observed this more severe form of localized peritonitis and the severity of adhesions has been reduced.

This Example illustrates that peritoneal implantation of low-bioburden implants reduces adhesions and does not result significantly in peritonitis in bovines other than in localized non-septic peritonitis. Use of sterile implants is expected to further decrease adhesions and further reduce the likelihood of septic peritonitis.

Example 3

This example illustrates manufacture and assembly of the invented device. Device 102 is molded out of an acrylonitrile-butadiene-styrene (ABS)(Lustran® 248 brand ABS available from Monsanto Company, St. Louis, MO) plastic with a white or a gray colorant added for appearance and to serve as a light barrier. The device has an overall length of 8.97" from the tip of the bevel to end of the device that is inserted into a gun for delivery.

The bevel has an approximately 30° angle and has one bevel of 34° and a second bevel of 5°. The tip of the bevel has been given a sharp point to facilitate penetrating the peritoneum, however, the heel of the bevel is dulled or rounded to eliminate coring.

Internal diameter at the bevel is 0.424" and is 0.48" at the end in which the seal resides during storage, thus producing a taper to facilitate molding. In the area in which the seal resides there is no taper to assure a seal between the device sidewall and the sidewall-engaging portions of the seal while the device in storage. At the seal end of the device a chamfer (See Figure 4A) facilitates loading of the implants and the seal.

At the end adjacent the beveled tip a retaining system incorporates a protuberance between two longitudinal slits 0.02" wide by 1.0" long. The protuberance begins to rise 0.66" from the tip of the device and is 0.021" above the inner diameter wall, thus reducing the opening from 0.424" to 0.407". The

protuberance has a radius of 0.25" as the implant begins to be discharged over the protuberance and a radius of 0.40" as it passes from the protuberance. The first radius retains the implant and the second radius facilitates ejecting the part from molding. The retaining system incorporates the protuberance height and ability to flex via the two longitudinal slits. Hence, the implant in this example has an outer diameter of 0.41" and is retained until the implant is expelled past the protuberance causing approximately 0.003" deflection in the protuberance without causing damage to the exterior of the implant.

The outer diameter of the device consists of two different diameters. The bevel end is 3.97", the proximal 0.5 inch is not tapered, and will maintain a 0.56" outer diameter for providing a seal surface when the sheath is applied. This end will be covered by the sheath and will remain sterile until the time of use. The second diameter is 5.0" in length and the outside diameter is increased to 0.68" at the shoulder and is tapered to 0.77" at the second end. However, the last inch has no taper to facilitate mounting in the administration gun. An indicating mark is added to the outer diameter to show orientation of the bevel to the user.

Polypropylene (Himont PD626 available from Himont, Wilmington DE) is used to mold the sheath and may or may not have a colorant added. The sheath covers the entire area that is to be inserted into the animal at the time of use. Total length of the sheath is 4.28" long and the outside diameter range from 0.61" at the closed end 0.68" at the open end. In the inside at the closed end is a protruding tubiform spacer long enough to keep the implant off of the protuberance during filling, shipping and storage.

In respect of the sheath, there are two proximal similar annular rings which rise 0.019" above the internal diameter of 0.6". Thus, a seal will be made between the trocar's outside diameters, of 0.561" and the inside diameter 0.558" of the sheath's sealing rings. A balance between the sterility seal and the removal force of the sheath is accomplished by the annular rings.

The seal is injection molded using Monsanto Santoprene and is 0.811" in length. There are two sidewall-engaging sealing rings with an outer diameter of 0.490" and which are 0.076" wide. The distal or front face of the seal has an extrusion or bumper of 0.273" long by 0.25 diameter that will insure that all implants have been pushed past protuberance 130 when the push rod has passed through its preferred range of motion. The seal has a hollow in its proximal end to accept a push rod of an administration gun to facilitate the seal's trueness as it travels down the interior of the device.

Example 4

This example illustrates the invented method of the invention. The left paralumbar fossa is cleaned of debris, alternatively hair clipped, and a 20 mm vertical incision is made to a depth required to pierce the hide (about 7-10 mm). The slit is placed preferentially in the exact center of the fossa, but may also be to areas caudal to this site. A disposable trocar is inserted through the slit, with the primary direction being perpendicular to the skin. Inclining the trocar during insertion is not recommended due to the possibility of injury to the loin area and/or possible implantation into kidney fat. However, the trocar can be tilted once insertion is completed. A distinctive feel and/or sound can sometimes be detected by experienced technicians when the peritoneal lining yields to the trocar tip. The implants contained in the trocar are

discharged to the peritoneal cavity and the trocar is withdrawn. The wound is permitted to heal with no additional attention or an antiseptic is applied to the surface of the wound.

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APPENDIX A

OSMOTIC SYSTEM FOR DELIVERY OF FLUID-SENSITIVE SOMATOTROPINS TO BOVINE ANIMALS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 07/513,361, filed April 20, 1990, which is a division of U.S. Ser. No. 07/283,359, filed December 13, 1988, now U.S. Pat. No. 5,034,229, which applications are incorporated herein by reference and benefit is claimed of their filing dates.

This application is also related to U.S. Ser. Nos. 512,301, filed April 20, 1990, now U.S. Pat. No. 5,174,999; 513,327, filed April 20, 1990, now U.S. Pat. No. 5,057,318; 513,328, filed April 20, 1990, now U.S. Pat. No. 5,037,420; 513,330, filed April 20, 1990, now U.S. Pat. No. 5,110,596; 513,363, filed April 20, 1990, now U.S. Pat. No. 5,135,523; and 513,528, filed April 23, 1990, now U.S. Pat. No. 5,059,423; all of which are divisions of U.S. Ser. No. 283,359 (above); 681,848, filed April 8, 1991, now abandoned, which is a continuation of U.S. Ser. No. 513,328 (above); 789,241, filed November 7, 1991, which is a continuation of U.S. Ser. No. 513,369, filed April 20, 1990, now abandoned; and 203,967, filed March 1, 1994, which is a continuation of 789,241 (above).

All of the above applications are assigned to ALZA Corporation, Palo Alto, California.

FIELD OF THE INVENTION

This invention pertains to both a novel and to an unobvious delivery system. Particularly, the invention relates to a delivery system that operates by osmosis and more particularly, the invention relates to a device that protects and administers a fluid-sensitive beneficial agent to a fluid environment.

BACKGROUND OF THE INVENTION

Delivery systems for administering a beneficial agent to a biological, fluid environment of use are known to the prior art. See, for example, U.S. Pat. Nos. 3,845,770; U.S. Pat. No. 3,916,899; 3,995,632; 4,111,202; 4,111,203; 4,203,439; 4,327,725; and 4,612,008.

The delivery devices described in the above patents operate successfully for their intended use and they can deliver many beneficial agents for their intended effects. Now, it has been observed that their use can be limited because they lack the necessary elements to deliver beneficial agents that are sensitive to fluids and to fluids containing biological gases. Their use may be limited because beneficial agents that are sensitive to such aqueous-biological fluids or to other fluids external to the delivery device may be adversely affected by fluids that enter the device and contact the beneficial agents during operation of the device. Examples of such fluid-sensitive agents include proteins, peptides, and hormones. Moreover, the prior art devices lack the necessary means for their use as implant devices for dispensing such sensitive agents to a biological fluid-rich environment of use.

It will be appreciated by those versed in the dispensing arts that if a delivery system is provided for administering at a controlled rate and for protecting a beneficial agent that is sensitive to aqueous and biological fluids, and which delivery system possesses the kinetic ability to deliver the protected beneficial agent in effective amounts over time, such a delivery system would have a positive value and represent an advancement in the dispensing arts. Likewise, it will be self-evident to those versed in the implant art that a pressing need exists for an implant that is essentially free of the tribulation associated with the prior art and that, if such an implantable delivery system is provided, it would have a practical application in the fields of human and veterinary medicine and in the breeding and management of farm animals.

SUMMARY OF THE INVENTION

The present invention is directed to a fluid-imbibing delivery device or dispenser for storing and protecting a fluid-sensitive beneficial agent and for dispensing the beneficial agent to a fluid environment of use. The device comprises a housing enclosing an internal compartment, the housing having a first wall section and a second wall section and, optionally, an end cap, the first wall section substantially restricting the passage of fluid into the delivery device, i.e. it is substantially fluid-impermeable, and the second wall section permitting the passage of fluid into the delivery device, i.e. it is fluid-permeable, in at least a portion. The device further comprises a beneficial agent in that portion of the internal compartment defined by the first wall section, expandable means for pushing the beneficial agent from the delivery device in that portion of the internal compartment defined by the second wall section, exit means in the first wall section or in the end cap, if an end cap is present, and, optionally, a partition layer, including a cantilevered piston member, between the beneficial agent and the expandable means, the partition layer being substantially impermeable to fluid. The device further optionally comprises forming the portion containing the beneficial agent of a material that reduces the adherence of the beneficial agent thereto. The device further optionally comprises a buttress to strengthen the joint between the first and second wall sections while smoothing the transition between the same.

One class of fluid-sensitive agents that are presently preferred for delivery from the devices of the present invention are growth factors, including bovine somatotropin and analogues and derivatives thereof. The devices of the present invention provide a means for delivering an effective amount of a beneficial agent for causing increased productivity, such as, in the case of the somatotropins, a higher feed conversion efficiency, improved carcass quality, higher than normal rate of animal weight gain, and increased milk production.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawing figures, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

FIG. 1 is a cross-sectional view of one embodiment of the delivery device of the invention, illustrating one structural embodiment of the delivery system comprising a first walled section and a second walled section.

FIG. 2 is an enlarged fragmented cross-sectional view of the mating end cap of FIG. 1.

FIG. 3 is an enlarged fragmented cross-sectional view of the tenon and mortise embodiment of the mating end cap of FIG. 2.

FIG. 4 is an enlarged fragmented cross-sectional view of the extending portion of the mating end cap and first wall section of FIG. 1 which maintains the exit passageway in contact with the beneficial agent.

FIG. 5 is an enlarged fragmented cross-sectional view of the joint between the first and second wall sections of FIG. 1;

FIG. 6 is an enlarged cross-sectional view of the piston member FIG. 1.

FIG. 7 is an enlarged top elevational view of the piston member of FIG. 1.

FIG. 8 is a graph showing the passage of water by the piston of FIG. 3 from the internal compartment surrounded by an impermeable first wall section into the internal compartment surrounded by permeable second wall section of FIG.1.

FIG. 9 is a graph showing the passage of water by the piston of FIG. 3 from the internal compartment surrounded by an impermeable first wall section into the internal compartment surrounded by permeable second wall section of FIG.1, excluding data ≥ three standard deviations from the mean

DETAILED DESCRIPTION OF THE INVENTION

In the following discussion, like reference numerals refer to like elements in the figures.

FIG. 1 depicts in opened view one embodiment of the delivery device according to the present invention. Delivery system 10 of FIG. 1 comprises a housing 11 formed of a wall 12, which wall 12 comprises a first wall section 12a and a second wall section 12b. Wall 12, comprising first wall section 12a and second wall section 12b, surrounds and defines an internal compartment 18. Delivery system 10 has at least one exit passageway 13 for delivering a beneficial agent 7 formulation from delivery system 10. Optionally, the exit passageway can be occluded with a material like that in seal 30, discussed below, that gets discharged, leaches or erodes during the time of use. In FIG. 1, delivery system 10 comprises a dome-shaped rear end 8 and a flattened lead end 9. In embodiments not shown, delivery system 10 can be manufactured with a pair of rounded or flat ends 8 and 9. The term "lead end", as used herein, generally denotes the end from which beneficial agent 7 is released from the system. In use, either the lead end or the rear end may be implanted first.

Wall section 12a may be in the form of an tubular member having a first and a second open ends 32 and 34, respectively. In this particular embodiment, an enclosure means 36 is positioned on first wall section 12a at its end lead 9. In this particular embodiment, the enclosure means is in the form of an end cap 38. The wall section 12a and end cap 38 together form passageway 13, seal 30 and surround that portion of internal compartment 18 that contains a beneficial agent 7 formulation.

Referring now to FIG.1, wall section 12b has a first or open end 40 and a second or enclosed end 42, the enclosed end at end 8 and the open end distant therefrom. Open end 40 defines and forms receiving means 19. Receiving means 19, having a first buttress 44 and second

buttress 46, is received within enclosing means 20 of first wall section 12a. First buttress 44 can be formed by providing the enclosing means 20 of the first wall section 12a with a first interior surface portion 48 having a first inner or bore diameter and a second interior surface portion 50 having a second inner or bore diameter, so that the internal buttress or interior annular ledge 44 is formed or defined where the first and second interior surface portions of wall section 12a meet.

Formed on the outer surface 52 of the wall section 12b is the second buttress 46. Second buttress 46 is positioned to abut with the second open end 34 of the first wall section 12a when the enclosing means 20 of the wall section 12a abuts with the first buttress 44. As a result, the second buttress 46 in combination with the first buttress 44 forms a double butt joint to mate the wall sections 12a and 12b for a strong joint while minimizing the external discontinuities or surface friction of the implant device and providing a smooth transition between the first and second wall sections. In this particular embodiment, the portion of the second wall section 12b inserted within the first wall section 12a has the same thickness as that portion outside the first wall section. In addition, as a result of this construction, the inside surface of the first and second wall sections facilitates the travel of the piston along the formed smooth continuous interior surface.

As best shown in FIG. 5, the buttress 46 includes a buttress engaging surface 54 for abutting with the first wall section 12a and an exterior or contoured surface 56 to smooth the transition from the exterior surface of the first wall section 12a to the exterior surface of the second wall section 12b. In the illustrated embodiment, when viewed in cross-section, has a generally s-shape. The contoured surface 56 includes a non-tapered annular portion 57, an annular convex portion 58 and a concave annular portion 60. In one particular embodiment, the contoured annular surface 56 includes a non-tapered annular portion 57 which extends distally away from the engaging surface 54 and towards

the end 8 a short distance, for example about 0.010 inches, generally parallel to the inside surface of the second wall section and has an outer diameter substantially equal to that of the first wall section 12a. This generally annular portion 57 terminates in and is integral with the convex annular portion 58, having a slope with a radius of about 0.115 inches. The convex portion 58 connects and is integral with concave annular portion 60, having a concave slope with a radius of about 0.300 inches. The concave annular portion 60 terminates in and connects with the outer portion 64 of the second wall section 12b having a different diameter, in this example smaller, than outer diameter of the first wall section 12a. As a result, the buttress 46 extends smoothly radially outward from the exterior surface of the second wall section to the exterior surface diameter of the first wall section, smoothing the transition between sections of the device having different outer diameters.

Wall section 12b surrounds that portion of internal compartment area 18 that contains a means 25 for expanding and for occupying space in compartment 18 for delivery of a beneficial agent formulation from delivery of a beneficial agent formulation from delivery system 10. The thickness and the surface area of the second wall section 12b contribute to the rate of passage of fluid through the membrane second wall section. In the preferred embodiment the second wall section or membrane cap 12b is aobut 1.442 inches long, and inner diameter of about 0.288 inches. The second wall section 12b has an over diameter of about 0.365 inches at the receiving end 19 and about 0.378 inches at the portion not inserted within first wall section 12a. A membrane cap of substantially these dimensions provide a desired fluid flow rate into the comprising the second wall section of about 10-15 mgH_2O/day and more particulariy about 12-14 wg H_2O/day. The two wall sections, sections 12a and 12b, at receiving means 19 and enclosing means 20 are close in size. There is clearance or tolerance in size to allow enclosing means 20

of wall section 12a a sliding movement over the receiving means 19 of wall section 12b and provide a small gap, preferably between 0.002-0.006 inches, between the wall sections so that a cyanoacrylate adhesive with good gap filling characteristics will wick to form a bond between 19 and 20. In one preferred embodiment, the outside diameter of the second wall section 12b is about 0.362 inches, and the inside diameter of the first wall section is about 0.365, providing a space of about 0.003 inches. Wall section 12a and wall section 12b can be telescoped completely until halted by buttresses 44 or 46 into a closed and continuous internal walled position. In the illustrated embodiment, optionally, optionally, a plurality of longitudinal ribs 66 formed upon the outer surface of the second wall section on the lead end or side of the engaging wall 54, space apart the first and second wall sections to define and form adhesive receiving cavities 68 between the first and second wall sections and in between the longitudinal ridges. Optionally, the wall sections 12a and 12b can be held together by heat fusion, by an adhesive, or the like. Preferably the adhesive is a cyanoacrylate adhesive having a low-enough viscosity to wick into the joint and form a secure bond. A cyanoacrylate adhesive having the same qualities and characteristics as that sold by Permabond of National Starch and Chemical Company under the brand name Permabond USP Grade 701 Adhesive is sufficient for the purposes of this invention. Buttresses 44 and 46 ensure that the juncture of 12a and 12b are smoothly and precisely joined in mated contact without discontinuities which would facilitate encapsulation of device 10.

Referring again to now to Figure 1, there is shown, as discussed in more detail with regards to Fig. 3, an embodiment of the mating end cap 38, adapting the end cap for ultrasonic welding to the first wall section 12a; and maintaining the exit passageway 13 in contact with the beneficial agent 7, while minimizing the dilution of the beneficial agent by adjacent body fluids present at the environment of use 41.

The end cap 38 is designed with specific features applicable to slow release implants osmotically driven being one specific type, that required pressure drop for the operation of the implant. The cap is specifically beneficial when delivering fluid sensitive materials and protects the material to be delivered before and after activation of the device. The engineered exit port that provides for a specific superficial formulation flow rate to eliminate dilution of the formulation by external fluids and maintains a required pressure drop for the operation of the implant. The engineered internal seal that provides point of use readiness without having to reopen the device also provides for a long term stability seal , protects formulation at start-up and has an engineered consistent rupture pressure for consistent startup. Designed headspace and internal configuration that minimizes internal pressure from thermal expansion of formulations an exit port that maintains contact with the formulation through all phases of the pump operation. Ultrasonic weld for application of the cap that is designed for automated application protection of formulations during the welding process, and gives a biocompatible joint seam as a result of a melt sink designed into the weld configuration.

As best shown in FIG. 1, end cap 38 includes a first end cap side 70, a second end cap side 72 and an exit passageway 13 extending from the external environment 41 into internal chamber 18. Exit passageway 13 is designed for an adequate formulation flow rate, driven by driving member 25 and a partition member 27 including piston 29 to prevent dilution of the formulation in chamber 18 by the inflow of fluids from external environment 41. Exit passageway 13 is also maintains the pressure drop for a given rate of release of the formulation from device 10. Exit passageway 13 is preferably designed so that the rate of outflow of formulation exceeds the rate at which fluids from the external environment diffuse inwards.

Referring now to FIG. 2, exit passageway 13 further includes first side 70 defining a first concentric exit aperture 74, in the preferred

embodiment having a diameter of about 0.075 inches. Second side 72 defines a second exit aperture 76, in the preferred embodiment having a second diameter of about 0.017 inches. Concentric communicating passageway 78, having the same diameter as the second exit aperture, fluidly connects the first exit aperture 74 with the second exit aperture 76 over a distance of about 0.100 inches to provide a means for the beneficial agent 7 to pass from the second side of the end cap to the first side of the end cap and out to the external environment 41. The diameter of the exit passageway 76 determines the velocity of the efflux or outward flow of the beneficial agent 7 from the portion of the internal compartment comprised of the first wall section 12a in the preferred embodiment, a passageway diameter of 0.017 inches is sufficient to generate a sufficient outward velocity of the beneficial agent therefrom. The length of the exit passageway provides a means for compensating for slight variations in the efflux or outward flow rate of the benefical agent. In one embodiment, a passageway length of 0.100 inches was sufficient. First side 70 includes an external face 80, the external face generally defining a plane substantially perpendicular to the longitudinal axis of the end cap 38. The communicating passageway 78 has a generally fustro-conically shaped contoured interior annular surface portion 79, smoothly joining the larger diametered first exit aperture 74 with smaller diametered communicating passageway 78 and second exit aperture 74. In one embodiment, the surface has a radius of about 0.028 inches, with a center 0.028 inches from the external face 80 and 0.028 inches from the surface of the communicating passageway 78.

Along its outer edge, the external face 80 joins with an annular concentric rounded portion 82 for rounding off the edges of the device. In this particular embodiment, the annual rounded portion 82 is defined by a radius of about 0.066 inches, with a center about 0.066 inches radially inward from the outermost edge 84 and about 0.066 inches inward from the end face 80.

As best shown in FIG 3, second side 72 of end cap 38 also includes a mating portion 86 for engaging or mating with the first wall section 12a, adapted for ultrasonic welding. The mating portion 86 includes an annular mating surface 88 on the second side 72 for engaging with the first wall section 12a, and a tenon 90 extending outward therefrom towards the first wall section 12a. In one particular embodiment, the annular tennon 90 has an annular thickness of about 0.018 inches, and is formed about 0.018 inches from the outermost edge 84 and extends outward from the mating surface 88 to terminate in an apex 92. The tennon 90 includes an first portion 94 that extends outward from the annular mating surface 88 a distance of about .026 inches. Apex 92 includes a pair of annular oblique faces 96 and 98 which are angled at about 28° from the vertical, i.e., a plane generally parallel to the longitudinal axis of the end cap 38.

As earlier described, first wall section 12a includes first open end 32. The open end 32 has an engaging surface portion 100 for engaging with the end cap 38. This surface or open end 100 defines a mortise 102 for receipt of the tennon 90 extending outward from the mating surface 88 of the end cap 38. In one particular embodiment, the mortise is defined by a first mortise wall 104, a second mortise wall 106 and a mortise bottom wall 108, the first and second walls 104 and 106 generally parallel to the longitudinal axis of the first wall section 12a and spaced apart about a distance of 0.030 inches. The mortise bottom surface 108 connecting the first and second side walls 104 and 106 at a depth of about 0.026 inches from the engaging surface 100 of the first wall section 12a.

Referring again to FIG. 1, it can be seen that end cap 38 is adapted with an inward extending portion 110 which defines a headspace 112 between wall 12a and end cap 38, such that when the end cap is engaged with wall 12a, defining chamber 18 which is filled with beneficial agent formulation 7, any resulting volume in chamber 18 which

does not contain formulation is confined to the headspace. In this way, regardless of the orientation of device 10, beneficial agent formulation is in contact with seal 30 or with exit passageway 13 and entrance of fluid into chamber 18 from external environment 41 is inhibited.

As best shown in FIG.4, second side 72 of end cap 38 also includes an extension 114 for sealing the exit passageway 13 and maintaining the exit passageway in contact with the beneficial agent 7 disposed within a portion of the internal chamber 18. The extension 114 includes a generally cylindrical portion 116, extending outward and integral with the annular mating portion 86 such that when the end cap 38 is mating with the first wall section 12a, the annular cavity 112 is defined therebetween to accumulate an air volume inserted or present in the internal compartment 18 to allow for differential expansion of beneficial agent and plastic within the interior chamber 18. The extension portion 114 at its terminal portion 118 includes an end cap apex 120. Apex 120 includes or defines therein a depot 122 for receipt of a sealant. A sloping contoured surface 124 extends and connects the annular mating surface 80 with the depot 122. In one embodiment, the sloping surface 124 is generally s-shaped in cross-section and includes a first concave annular portion 126, a second concave annular portion 128, and a convex annular portion 130 forming a generally s-shaped surface in cross-section. In one preferred embodiment, the first concave annular portion 126 has a slope generally defined by a radius of about 0.029 inches from a center 0.125 inches radially outward from the central longitudinal axis and 0.083 inches along the central longitudinal axis from the apex 120 on second side 72. The second concave annular portion 128, integral with and extending radially inward from the first concave annular portion 126, joins with the convex annular portion 130, and has a slope generally defined by a radius of about 0.125 inches from a center at 0.200 inches radially outward from the central longitudinal axis and 0.026 inches along the central longitudinal axis from

the apex 120 on the second side 72. The convex apex portion 130 has a slope generally defined by a radius of about 0.026 inches from a center 0.026 inches radially outward from the central longitudinal axis of the end cap 38 and the apex 120 on the second side 72 in addition FIG. 4 illustrates that after welding of the end cap 38 to the first wall section 12a, the outer surfce of the tenon 90 may be altered by the welding procedure to generally assume a shape similar to that of the mortise 102..

Depot 122 is comprised of the apex 120 defining a depot bore 132, for receipt of the sealant 30, the depot bore in fluid communication with the interior chamber 18 and the exit passageway 13. In the preferred embodiment, the depot bore 132 is defined by a generally cylindrical first or bore side interior surface 134 and a generally planar bottom surface 136, the bore having a diameter of about 0.100 inches and a depth of about 0.050 inches. The bore side surface 134 slopes generally inward towards the longitudinal axis of the end cap 35 as the surface extends from the end proximal to the second exit aperture 76 to the end distant from the exit aperture at an oblique angle. In the preferred embodiment, the oblique angle is about 2° from the axis parallel to the central longitudinal axis of the end cap 38.

In the handling and operation of the device, the relationship between headspace 112, depot 122 and exit passageway 13 plays a significant role. Headspace 112 permits contraction and expansion of the formulation 7 in device 10 during shipping and handling and also provides for the buildup of pressure in device 10 after implantation into an animal. Headspace 112 insures that any air left in the formulation is not in the formulation where it can form a bubble adjacent to exit passageway 13 but is confined to head space 112. If a bubble were permitted to form adjacent exit passageway 13, then when pressure built up sufficient to expel the plug in depot 122, an inflow of fluid from the external environment could dilute the formulation and the rate of delivery of

formulation from device 10. In filling the device, heat treatment after filling assists in "setting" the formulation, locking the air bubble into place in headspace 112 where it will not affect initial operation of device 10.

Figure 6 illustrates in greater detail piston 29 of Figure 1. Piston 29 is an elastomeric piston generally cylindrical in shape which incorporates first and second deformable seals 140 and 142. Piston 29 provides a high interference seal with minimum lateral force applied to the device wall which would impede longitudinal travel of the piston. The deformable seals 140 and 142 compensate for any irregularities in the internal wall of device 10 to provide an effective seal. The piston material, in one preferred embodiment, can be formed of any of four grades of Santoprene © 271 material, the most preferred grade being 271-55.

In one embodiment, the piston 29 includes a cylindrical body portion 145 positioned within the first wall section 12a. The piston 29 includes the cylindrical first or central body member 145 with first and second piston ends 144 and 146 respectively. The deformable seals 140 or 142 are formed at first and second piston ends 144 and 146 respectively. In one particular embodiment, the deformable seals 140 and 142 include a flared, conical skirt member or section 148. As best shown in FIGS. 6 and 7, the skirt 148 extends radially outward from the central body member 145 to terminate at a position spaced apart therefrom. Referring again to FIG. 6, a metal location detection member 150 is formed within the central cylindrical body member 145. The skirt member 148, extends radially outward a distance of about .016 inches from the respective piston end surface to extend longitudinally a distance of about .079 inches at an oblique angle of about 15 degrees from the plane generally defined by the surface of the central body member 145. As a result, the distal end of the piston 29 are biased radially outward when articulating within the inner diameter of the first wall section 12a. The thickness of the skirt enables the skirt to provide sufficient wiping

pressure to the inside surface of the first wall section without invoking such pressure as to cause the skirt to fold over.

Referring again to FIG. 5, first wall section 12a at its end distant from lead end 9 defines and forms an open end having a circumference for forming a lap joint 152 with wall section 12b. Second wall section 12b defines rear end 8 and it surrounds that portion of internal compartment 18 which initially contains an expandable driving means, here illustrated by expandable driving members 25a-f. Second wall section 12b at its end distant from rear end 8 defines and forms an open end having a circumference for forming lap joint 152. Second wall section 12b is adapted with buttress 56 for strength and precision of manufacture. Preferably the buttress is shaped to provide a smooth surface transition between wall sections 12a and 12b to minimize irritation leading to encapsulation.

Lap joint 152 includes, in the illustrated embodiment, lap joints 152a and 152b, reciprocally received one within the other for mating engagement when the two edges are assembled together. The lap joints 152a and 152b are of such a design as to provide a strong mechanically and hydrostatically intact seal when they are bonded together with an adhesive, such as a pressure-sensitive contact adhesive, a moisture-curing adhesive, an ultraviolet-curing adhesive or the like. While FIG. 1 shows the two wall sections assembled with the lap joint 152a of first wall section 12a enclosing the outside of the lap joint 152b of second wall section 12b, this arrangement is not critical and may be reversed. However, the illustrated embodiment is preferred since it provides additional restraint on the second wall section or membrane cup 12b pulling away from the lap joint. In addition, if the material used in the formation of the wall section surrounding the osmotic driving member, for example wall section 12b, is not as strong as the material used in the formation of the portion surrounding the beneficial agent 7, for example first wall section 12a, then the weaker material is preferably positioned

or disposed to the inside or inserted within the stronger material. For example, if cellulose acetate butyrate is used for the portion surrounding the osmotic driving member and polypropylene is used to surround the beneficial agent 7, then the cellulose acetate butyrate wall is preferably on the inside of the polypropylene wall.

In one embodiment of delivery device 10 as illustrated of FIG. 1, the system is manufactured as an implant comprising a body length of about 8.7 cm, a diameter of the first wall section of about 10.5 mm, a diameter of the second wall section of about 9 to 10.5 mm, a beneficial agent 7 formulation occupying a length of about 45 mm, an initial total length of about 26.54 mm, occupied by the expandable driving members, and an exit passageway of 2.5-2.6 mm in length and having a diameter of 0.017 inches. This diameter has been found effective to restrict flow of materials inwardly from the environment of use which the device is in use. In a presently preferred embodiment, the exit passageway 13 and depot 122 are occluded with a material such as wax that gets discharged, leaches or erodes when placed in the organic environment of use. The implant can be implanted into the peritoneal cavity using an implanter.

Generally, an implanter comprises a tubular member with a central longitudinal axial bore, a pointed, elongated, annular concavely beveled implanting end and an implant-charging end. The implanting end and the charging end communicate through a bore. A plunger adapted to be removably inserted in the bore is designed for slidable movement therein for applying the necessary force for implanting the implant. Alternatively, the implant can be surgically or subcutaneously implanted in the peritoneal cavity.

Referring again to Fig.1, first wall section 12a comprises a composition that is substantially impermeable to the exchange of fluid, beneficial agent 7 and other ingredients contained in delivery system 10. Wall section 12a, in a presently preferred manufacture, is substantially

impermeable to the ingress/loss of an external/internal fluid to serve as a means for substantially protecting a beneficial agent 7 that is sensitive to exterior fluid present in the environment of use. Wall section 12a substantially restricts and prevents fluid from passing through wall 12a and entering into compartment 18 in the region containing a beneficial agent formulation. In one particular embodiment, when used in conjunction with bovine growth factors, including bovine somatotropin, wall section 12a may be formed of a material which provides a reduced adherence of the beneficial agent 7 to the wall 12a. For example, the use of polypropylene in the construction of wall 12a will reduce the adherence of bovine somatotropin to the surface of wall 12a.

In the preferred embodiment, wall section 12a is formed of polypropylene because of its excellent low permeability to water and because of its low surface tension which facilitates non-adhesion of beneficial agent 7 to the internal surface as compared with other materials such as polycarbonates, which empirically appeared to result in increased bearding on the respective wall surface /beneficial agent interface, especially when the beneficial agent included bovine somatotropin. Preparing polypropylene for bonding preferably includes preparing the surface thereof to increase the likelihood of an effective seal. Those skilled in the art will recognize that this may be performed by various methods, a non-inclusive list includes, for example, by priming with a chemical primer, abrading or knurling the surface, treatment with plasma and the like.

Second wall section 12b is permeable to the passage of fluid in at least a portion and it is substantially impermeable to the passage of other ingredients contained in delivery system 10.

Wall sections 12a and 12b optionally comprise a plasticizer that imparts flexibility and workability to the wall. Wall 12, comprising sections 12a and 12b, is nontoxic and, in a preferred embodiment, it

maintains its physical and chemical integrity; that is, wall 12 does not erode during the dispensing period.

Compartment 18 comprises a beneficial agent 7 formulation, which beneficial agent 7 formulation comprises a beneficial agent 7, identified by dots, and a pharmaceutically acceptable carrier 21, identified by wavy lines. The pharmaceutically acceptable carrier may include more than one ingredient, such as a buffer 22, identified by horizontal dashes; a pharmaceutically acceptable vehicle 23, identified by vertical lines; a pharmaceutically acceptable surfactant 24, identified by slanted lines; and other formulation ingredients, as are known in the art.

Compartment 18 further comprises an expandable means or expandable driving member 25 optionally comprising members 25a-f. Expandable driving member 25 optionally comprises an osmagent homogeneously or heterogeneously blended with binder to form expandable driving member 25.

Compartment 18 may optionally comprise a partition layer 27. Partition layer 27 may optionally include, as in this embodiment, a piston 29, discussed in more detail with respect to Fig. 5. The partition layer 27 may include a portion which may be positioned between the drive piston 29 and the expandable driving member 25. The partition layer may comprise a composition that is substantially impermeable to the passage of fluid, and it further may act as a seal and restrict the passage of fluid present in the expandable driving member into the beneficial agent 7 formulation. Piston 29, alone or in cooperation with other portions of the partition layer 27, operate to essentially maintain the integrity of the beneficial agent 7 layer and the driving member layer 25. Portions of the partition layer 27 acts also to insure that the expanding driving force generated by the expandable driving member 25 is applied directly against piston 29 and thus is exerted on the formulation in compartment 18.

In operation, as the expandable member 25 absorbs and imbibes fluid through fluid-permeable second wall section 12b from the environment of use, it expands and pushes against piston 29 causing piston 29 to slide inside compartment 18. The piston may be lubricated, for example, using a silicone lubricant having the same characteristics as DOW 360 medical fluid 1000 cs. Piston 29 moves towards exit passageway 13, driving the beneficial agent 7 formulation in chamber 18 through passageway 13 for delivering the beneficial agent 7 to the environment of use. Second wall section 12b is telescopically capped by the engaging first wall section 12a. The two sections can be joined together by adhesive bond or various techniques such as solvent weld, thermal weld, ultrasonic weld, spin weld, induction weld, mechanical lock or by similar welding or bonding operations which may also be used in appropriate cases.

Delivery device 10 in FIG. 5 further comprises lead end 9, rear end 8, internal compartment 18, beneficial agent 7, pharmaceutically acceptable carrier 21, pharmaceutically acceptable buffer 22, pharmaceutically acceptable vehicle 23, and a pharmaceutically acceptable surfactant 24. In addition, a salt such as Na Cl or KCl may be present in amounts of 1-4 % by weight to assist stabilizing the state of formulation.

In a presently preferred embodiment, delivery device 10 comprises a plurality of expandable driving members 25a-f initially housed in second wall section 12b. This configuration is merely illustrative and there may be any number of driving member present. Generally, there are from one to six expandable driving members; however, this number is not controlling. The expandable driving members in a presently preferred embodiment are formed as depots or layers and comprise like or unlike compositions. For example, driving members 25a-f can be made as tablets comprising like osmopolymers or like osmagents, or they can comprise unlike osmopolymers or unlike osmagents, or one or more of the

members can be a composition comprising an osmopolymer together with an osmagent. The members can be the same or they can be different.

Referring again to Figure 1, end cap 38 further comprises a depot 122 in fluid communication between internal chamber 18 and exit passageway 13. Depot 122 can receive a material which is discharged, leached or eroded away during use. Preferably the material is wax or another material which can be discharged and depot 122 is sized to provide for sufficient present to discharge the material through passageway 13. This material serves several purposes: it seals delivery device 10 to prevent premature delivery of a beneficial agent 7 from delivery device 10 and to prevent evaporation of carrier components such as water during storage, it helps maintain the clean or optionally sterile environment inside delivery device 10, and it protects the ingredients inside the delivery device from oxidation by air and also protects the beneficial agent 7 from dilution by body fluids following implantation. More particularly, the seal 30 consistently releases at the same pressure using a 145 A wax in an end cap construction as described elsewhere in this application. In one preferred embodiment, the seal 30 releases at a pressure greater than 5-10 psi, more preferably greater than about 9 psi.

First wall section 12a, which surrounds the internal space of compartment 18 initially occupied by the beneficial agent 7 formulation, comprises a composition that does not adversely affect the beneficial agent 7, the osmopolymer, the osmagent, other ingredients in device 10, the host, or the like. First wall section 12a comprises a composition comprising means that substantially limits or prevents the passage of an external fluid into device 10. The phrase, "substantially limits or prevents," as used herein, indicates the volume of external fluid passing through first wall section 12a is substantially negligible, that is, about zero up to about 1 μL per day (see example __ discussed more fully elsewhere in this application). Typical compositions for forming first section 12a are discussed in U.S. Patent Nos. 5,057,318 for example.

The second wall section 12b comprises a composition comprising means that aid in controlling fluid flux into the compartment area occupied by the expandable driving member 25. The composition is semipermeable; that is, it is permeable to the passage of external fluids such as water and biological fluids and it is substantially impermeable to the passage of beneficial agents, osmopolymers, osmagents, and the like. Typical compositions comprising semipermeable materials for forming wall 12b are known in the art, a non inclusive list includes the group consisting of a cellulose ester, a cellulose ether and a cellulose ester-ether, including, for example, cellulose acetate butyrate. These cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit from greater than 0 up to 3, inclusive. By "degree of substitution" or "D.S." is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative fluid-permeable materials are discussed in U.S. Patent Nos. 4,874,388, 5,034,229, and 5,057,318, for example. The amount of semipermeable materials presently preferred in wall 12b is from about 20% to 100%. In the presently preferred form, the wall is formed of polypropylene equivalent to medical grade polypropylene PD626 sold by Himont, because of its excellent low water transport qualities and the relative low surface tension relative to the beneficial agent 7 formulation as compared to other polycarbonates, especially when the beneficial agent is bovine somatotropin.

Representative materials that can be used to regulate further the fluid flux of wall 12b include materials that decrease the fluid flux and materials that increase the fluid flux of wall 12b. Representative materials optionally added to wall 12b for either decreasing or increasing the flux are presented in U.S. Patent Number 5,034,229 and 5,135,523.

First wall section 12a and second wall section 12b optionally comprise a nontoxic plasticizer. Representative plasticizers suitable for

forming wall 12a or wall 12b are well known in the art and examples are presented in U.S. Patent Number 5,034,229 and 5,135,123.

Delivery device 10 in its compartment 18 can also comprise pharmaceutical carrier 21. Carrier 21 may optionally include viscosity modulating vehicles (23), buffers (22), surfactants (24), dyes, and other additives known in the art, examples of which are disclosed in U.S. Patent Number 5,034,229 and 5,135,123 to comprise the beneficial agent 7 formulation.

In a presently preferred embodiment, the beneficial agent 7 is bovine somatotropin, in an amount of from about 25% to about 60% by weight (wt%) of the beneficial agent 7 formulation, preferably from about 30 wt% to about 45 wt%.

The expandable driving means 25 initially surrounded by second wall section 12b and operable for pushing the beneficial agent 7 composition 20 from delivery device 10 comprises, in a presently preferred embodiment, an osmopolymer. The osmopolymers interact with water and aqueous biological fluids and swell or expand to an equilibrium state. The osmopolymers exhibit the ability to swell in water and to retain a significant portion of the imbibed and absorbed water within the polymer structure. The expandable driving member 25 in another preferred embodiment comprises an osmagent. The osmagents are known also as osmotically effective solutes and they are also known as osmotically effective compounds. The osmotically effective compounds that can be used for the purpose of this invention include inorganic and organic compounds that exhibit an osmotic pressure gradient across a semipermeable, i.e. a fluid permeable, wall. The expandable driving member 25 yet in another preferred embodiment comprises an optional osmagent dispersed within the osmopolymer. The osmagent or osmopolymer can comprise a tablet or a layer or can be pressed into second wall section 12b. The osmagent or osmopolymer can be in any suitable form such as particles, crystals, pellets, granules,

and the like, when pressed into a tablet layer and into wall section 12b. Osmagents and osmopolymers are known to the art in U.S. Patent Nos. 3,865,108, 4,002,173, 4,207,893, 4,327,725, 4,612,008, 5,034,229, and 5,135,123 for example.

Piston 29, positioned between the beneficial agent composition and the expandable driving member 25, is a means for maintaining the separate identity of the beneficial agent composition and the driving member, for transmitting the force generated by the driving member against the beneficial agent composition, and for substantially restricting the passage of fluid between the beneficial agent composition and the driving member.

End cap 35, illustrated in FIG. I, provides a means for simply and conveniently assembling the device of the invention, and particularly for filling the device with internal components such as the driving members, the partition and the beneficial agent formulation. The end cap 38 is impermeable to fluid, providing protection for the fluid-sensitive beneficial agent. Materials for forming end cap 38 may be chosen from those materials useful in preparing impermeable first wall section 12a.

The terms "exit means" and "exit passageway", as used herein, comprise means and methods suitable for the metered release of the beneficial agent 7 from compartment 18 of delivery device 10. This includes maintaining sufficient efflux or outward velocity of the beneficial agent to prevent an inward flow of fluid from the external environment to dilute the beneficial agent formulation in the portion of the compartment comprised by the first wall section. The exit passageway 13 includes at least one passageway, orifice, or the like, through first wall section 12a for communicating with compartment 18. The expression "at least one passageway" includes aperture, orifice, bore, pore, porous element through which the agent can migrate, hollow fiber, capillary tube, porous overlay, porous insert, and the like. The expression also includes material that gets discharged, erodes or is leached from the wall in the fluid

environment of use to produce at least one passageway in delivery device 10. The expression includes structural characteristics that concentrate stress at a precise point in the wall so that only a small amount of force will induce breakage in the wall, yielding a passageway through the wall from compartment 18 to the outside of the device. A passageway or passageways can be formed by the discharge, as a result of the pressure created by the expandable member for example, of a material such as a wax. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of beneficial agent from delivery device 10. Delivery device 10 can be constructed with one or more passageways in spaced-apart relations or more than a single surface of a dosage form. Passageways and materials, equipment and methods for forming passageways are disclosed in U.S. Patent Number 5,034,229.

EXAMPLE 1

Delivery device 10 can be manufactured by standard manufacturing techniques. In one process, the first wall section 12a and the second wall section 12b are independently injection molded or extruded into the desired shape. Then, the first wall section 12a is filled with the beneficial agent composition. The second wall section 12b is filled with an expandable driving member or members, and the piston 29 is next added thereto in layered arrangement. Optionally, the piston 29 may be added to the first wall section 12a after filling the wall section with beneficial agent, in addition to, or instead of, the partition layer added to second wall section 12b. Next, the two sections at their open ends are slid together.

The delivery device of the present invention can be manufactured for delivering numerous beneficial agents, including drugs, at a controlled rate to a presently preferred biological environment of use such as warm-blooded animals, including humans; ruminants, such as bovines and

sheep; porcines, such as hogs and swine; horses; and the like. The delivery devices provide for high loading of a beneficial agent and for its improved delivery in beneficially effective amounts (that is, amounts that provide a beneficial effect) over time. It is to be understood that the delivery devices can take a wide variety of shapes, sizes and forms adapted for delivering beneficial agents to environments of use. For example, the devices manufactured as delivery devices can be used for dispensing a beneficial agent in the anal-rectal passageway, in the cervical canal, as an artificial gland, in the vagina, as a subcutaneous or intraperitoneal implant, and the like. The delivery devices can be used in hospitals, nursing homes, outpatient clinics, sickrooms, veterinary clinics, farms, zoos, and other environments of use.

DETAILED DESCRIPTION OF EXAMPLES

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

A delivery device manufactured in the shape of an implantable delivery device according to the present invention is manufactured as follows.

An expandable driving member was prepared by first adding 10 liters of water and 526 g of polyvinylpyrrolidone to a stainless steel container and mixing the components for 1 hr to obtain a smooth binder solution. Next, approximately 20 kg of sodium chloride was milled in a mill to a number 21 size mesh screen. Then, 17.5 kg of the milled sodium chloride and 7.5 kg of sodium Carbomer®, a sodium salt of a polyacrylic polymer, were transferred to the granulator bowl of a fluid bed

granulator and 2.46 kg of binder solution was slowly sprayed onto the materials in the granulator. Granules were formed in this manner. Next, the granulated material was sized by forcing it through a 0.0469 in mesh screen in a screen separator. Then, the granulation was divided into two 12.8 kg sub-batches. For each sub-batch, 130 g of magnesium stearate was added and the ingredients were blended for 3 min at 9 rpm to produce a homogeneous expandable driving composition. The composition next was pressed into osmotically active tablets in a tablet press at a pressure of 2,000 lbs to produce a round, flat-faced 266 mg tablet as an expandable driving member .

The semipermeable wall (membrane cup) that surrounds a compartment for containing the osmotically active tablets was prepared as follows. First, 1.0 kg of tributyl citrate and 9.0 kg of cellulose acetate butyrate were dry mixed in a mixer for 30 min. This produced a polymer/plasticizer blend of 90/10 ratio for the rate-controlling semi-permeable second wall section 12b. The blend was then injection molded into a semi-permeable membrane cup of the desired shape with an open end for receiving an expandable driving member and for mating with the forward wall section, whose preparation is as follows.

The impermeable first wall section 12a of the delivery device 10 which forms the compartment holding the beneficial agent 7, is prepared by blending the polypropylene (Himont PD626) with a blue colorant (0.1 % FD & C blue lake). The mixture is then injection molded into the first or forward impermeable wall section 12a in the desired shape, with the open second end 34 for mating with the semi-permeable second wall section or membrane cup 12b and an open forward or lead end 32 for the end cap 38 . That portion of the first wall section 12a which mates with the semi-permeable second wall section or membrane cup 12b is molded with a diamond shaped pattern over a portion of its surface to enhance the adhesive bond between it and the membrane cup. Surface preparation ensures satisfactory adhesive bonding of polypropylene to

other materials. In the case of the first wall section 12a, in addition to the mechanical configuration described above, this may be accomplished by either applying a primer to the glue-joint area or by treating the surface with a plasma made from a mixture of oxygen and tetrafluromethane gases prior to applying the adhesive. That mating portion of the first or forward wall section which mates with the end cap 38 is molded with circumferential, rectangular-shaped mortise 102 to facilitate ultrasonically welding the end cap 38 to the forward wall section 12a as described more fully elsewhere in this application.

The end cap 38 was prepared by blending polypropylene (Himont PD626) with a blue or white colorant (0.1% FD & C blue lake or 1.0% titanium dioxide, respectively). This mixture is then injection molded to form the end cap 38, as described more fully earlier in this application, having the exit aperture with a 0.017 inch diameter approximately 0.1 inches long, an internal cavity for containing a wax sealant material, and a precisely determined circumferential configuration around the outer perimeter of the end cap 38 to facilitate ultrasonic welding of the cap to the forward wall section 12a. This configuration includes a wedge shaped energy director with an included angle of 56°, which is beneficial to achieving a high quality ultrasonic weld with crystalline, polymeric materials being joined. The internal cavity is filled with molten wax (Witco 145), which solidifies to form a seal to the orifice port.

The piston 29 is prepared by insert injection molding Monsanto brand thermoplastic elastomer sold under the brand name "Santoprene ® 271-55", into the piston with a circumferential, cantilevered lip at each end and a metal detection core in its center. The metal core is cylindrical in shape with a flat face at each end and is manufactured in a separate process by sintering at 1300° F a metal alloy consisting of nickel and iron in a 50/50 ratio. The metal core is inserted into the mold when it is in the open position, and the thermoplastic elastomer is injected around it during the injection molding process. The piston 29 thus formed is

lubricated with silicone medical fluid to facilitate movement of the piston inside the device during assembly and operation and to minimize piston set during storage.

The delivery device 10 is partially assembled by first charging the second wall section or semi-permeable membrane cup 12b with six of the osmotic tablets 25a-f. The second wall section 12b is then partially inserted into the impermeable first or forward wall section 12a of the device 10 and two drops of moisture-cured cyanoacrylate adhesive are dropped onto the exposed portion of the joint between the first and second wall sections, where the adhesive is drawn into the remainder of the joint by capillary action. The first and second wall sections 12 and 12b are then fully inserted to form a mechanically strong, water-tight seal. The lubricated piston 29 is then inserted through the remaining open end 32 of the first or forward wall section 12a, using a tool which allows air to pass by the piston 29 as it is moved into position against the osmotic tablets 25a-f and insert the piston within the wall section without having the skirtmember rolled. The tool used is a thin-walled funnel open at both ends having an internal chamber for receipt of the piston therein.

Next, the delivery device subassembly, comprised of the second wall section or membrane cup 12b, the osmotic tablets 25a-f, the impermeable first or forward wall section 12a and the piston 29, is filled with 2250 mg of the beneficial agent 7 formulation at 35° C. The formulation is comprised of 36.5 % ± 1.5% for Zn-bST in a phosphate buffer, glycerols, wetting agent, salt excipient blend where the w/w/w/w proportions of phosphate buffer, glycerol, Tween-80, and KCl are 48.38/48.38/0.24/3.0 respectively. The phosphate buffer is 60:40 monobasic:dibasic sodium phosphate, and the molarity is 0.45. Then, a waxed end cap 38 is place into position on the open lead end 9 of the first wall section 12a by ultrasonic welding. The filled implant 10 is heat

treated after being placed into a sterile package, for example, by heating the about 40° C for about 16 hours.

EXAMPLE 2

The pistons according to the invention were tested as follows:

A formulation of ZnbST in a phosphate/glycerol/Tween/NaCl excipient was prepared using titrated water (^3H_2O). The specific activity of the labelled water was 1.0 mCi/ml, and should be sufficient to provide a detection limit of 1 μgm of water. The formulation was loaded into 10 mm osmotic implants with two different piston designs (1.0x and 1.5x), and a third group that had the compartment surrounding the osmotic driving member prehydrated.

TABLE 1 - Pump configurations

Group	Piston	Pre-hydration
1	1.0x	no
2	1.5x	no
3	1.0x	yes

The implants were sampled in duplicate for group 1, and triplicate for groups 2 and 3, at intervals of 0, 3, 6, 12 and 18 weeks. For measurement of total water transport to the osmotic driving members, e.g. salt tablets, of the internal chamber 18 surrounded by the semi-permeable wall section 12b, the second wall section 12b was separated from the first wall section 12a and the end cut off. Salt tablets were expelled and dissolved in water. An aliquot of the solution was added to the liquid scintillallation cocktail and counted by standard liquid

scintillation counting techniques. Table 2 lists the individual measurements of the total water content.

TABLE 2

TRANSPORT OF WATER FROM THE FORMULATION COMPARTMENT TO THE ENGINE COMPARTMENT DURING STORAGE AT 4 C

Group/ Replicate	Week 0	Week 3	Week 6	Week 12	Week 18
1/1 130	12	37	75	7413*	
1/2 148	12	50	68	98	
1/3 162	-	-	-	-	

Group/ Replicate	Week 0	Week 3	Week 6	Week 12	Week 18
2/1	460*	43	66	331*	515*
2/2	14	41	67	97	150
2/3	1209*	45	235*	102	146
3/1	4	56	82	114	189
3/2	101*	46	65	711*	230*
3/3	5	51	76	112	139

* possible statistical outlier (greater than 3 standard deviations from mean excluding theses points).

Figure 8 is a graph depicting the relationship between μgms of H_2O

by-passing the piston versus time (weeks).

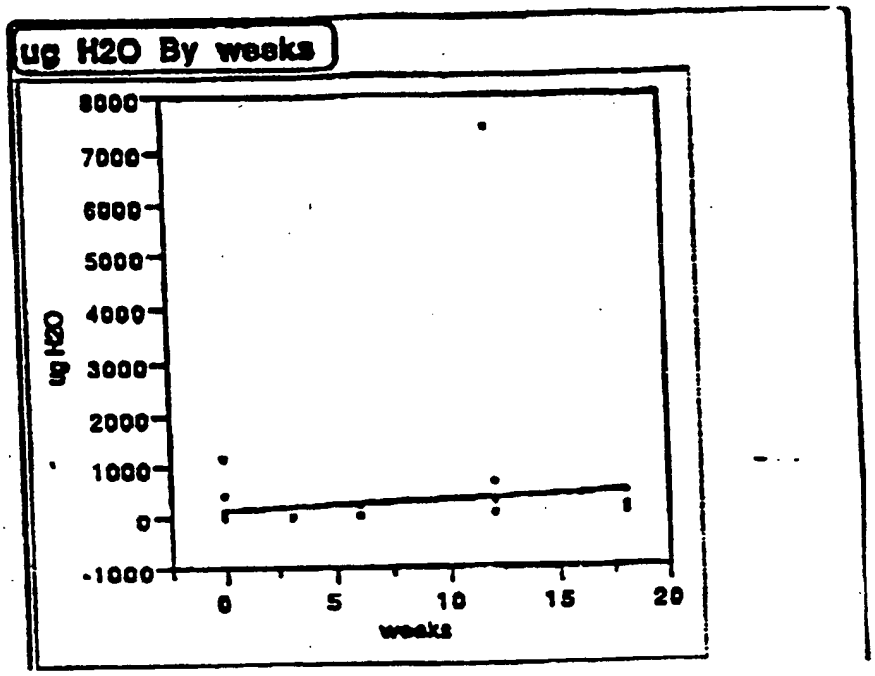
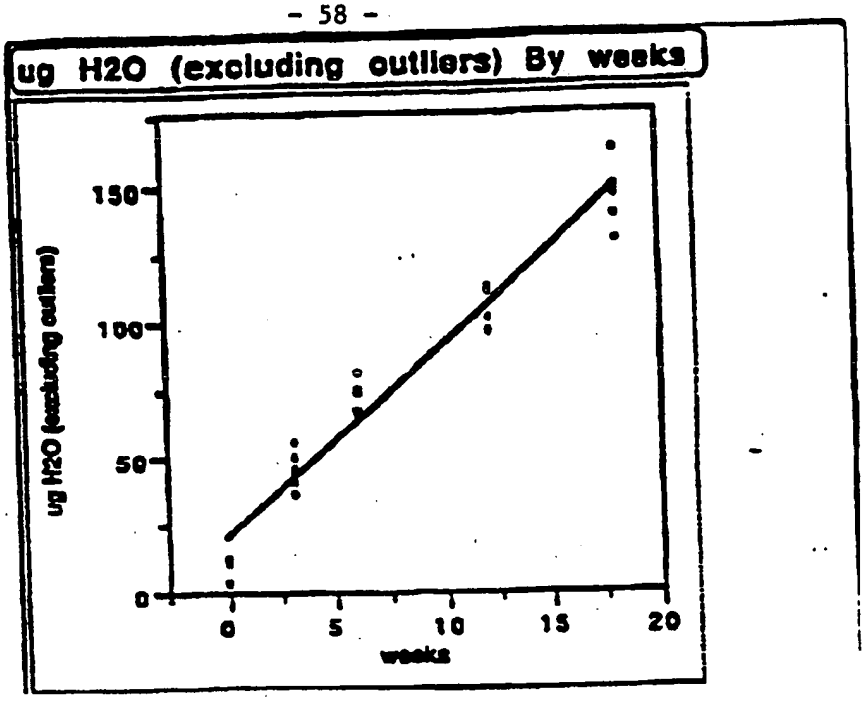


Figure a is a graph showing μgms of H_2O by-passing the piston versus time excluding outliers.



A variable amount of water (0.1-7 mg) transferred from the portion of the internal compartment 18 surrounded by the first wall section 12a to the portion surrounded by the second wall section 12b during the filling procedure for approximately 25% of the implants 10. There was a high pump to pump variability at all time points, on top of a small increase due to subsequent water transport from the internal compartment surrounded by the first wall section 12a to the salt tablets. The linear regression estimates of the rate of water transport along with 95% confidence intervals were as follows:

All data included:	20.0 ± 8.9 μgms/week
excluding outliers:	7.1 ± 0.1 μg/week

Thus, the worst case estimate (upper 95% confidence interval with all data included) was 28.9 μgms per week, or approximately 1.5 milligrams per year. The best case estimate (lower confidence interval excluding outliers) was 7.0 μgms per week, or 0.36 milligrams per year. Therefore

it was concluded, assuming the acceptable limit set by the amount of water that can be lost from the formulation without exceeding a 1 % increase in protein assay, is approximately 60 milligrams, that the piston tested in these experiments was deemed adequate to maintain separation between the portion the internal compartment 18 surrounded by the first wall section 12a and the portion of the internal compartment 18 surrounded by the semipermeable second wall section 12b for the anticipated shelf life of five years or more.

EXAMPLE 3

Delivery devices according to the present invention were tested in vivo as follows.

Example 3a (11466) -- Weekly Subcutaneously Administered Pellets

A study was undertaken to determine the effect of 40 or 80 mg A-bST pellets administered subcutaneously weekly during a 84-day beef cattle study on 1) growth, 2) feed efficiency and 3) carcass composition.

One hundred eighty Angus X Hereford beef steers weighing approximately 350 kg (770 lbs) were used. Stocking density was 5 animals per pen. The trial consisted of 180 steers with replicates of 12 pens (60 animals) per treatment group (control, 40 mg bST/wk, and 80 mg bST/wk). The study lasted 84 days (12 weeks) exclusive of the pretreatment period. The diet for all animals, on a dry matter basis, contained 16% crude protein ("P"). Potable water was available ad libitum. Pens were randomly distributed among treatments:

TABLE 3

Trial	Group	Treatment Pens	Animals	Description
1	1	12	60	Control

1	2	12	60	40 mg/wk A-bST Pellets
1	3	12	60	80 mg/wk A-bST Pellets

The animals were slaughtered for carcass analysis. The results are shown on the following Table:

TABLE 4

TREATMENT

Parameters	Control	40 mg/wk bST Pellets	80 mg/wk bST Pellets
Initial Body Wt (kg)	390.3	390.3	390.3
Final Body Wt (kg)	499.5a	495.0a	510.4b
Carcass Wt. (kg)	308.3	304.3	312.2
Dressing Percent	61.7	61.5	61.2
Carcass Gain Response	--	No Gain	39%
Non-Carcass Gain Response	--	No Gain	61%

a, b - different superscripts indicate that numbers in a row are significantly different ($p < .05$)

It was observed that neither dressing percentage nor carcass weight were significantly increased. Further, at a higher dosage, most of

the increase in body weight due to bST treatment was allocated to the non-carcass components.

Example 3b -- Weekly Subcutaneous or Intraperitoneal Pellets

A study was undertaken to determine whether the effect of 80 mg A-bST pellets during an 84-day beef cattle study was comparable when administered subcutaneously and intraperitoneally.

Two hundred seventy Angus X Hereford beef steers weighing approximately 350 kg (770 lbs) were bought and divided into three study groups. Stocking density was 5 animals per pen. Each study group consisted of replicates of 6 pens (30 animals) per treatment group (control, 40 mgbST/wk subcutaneous pellet, and 80 mgbST/wk intraperitoneal pellet). The study lasted 84 days exclusive of the pretreatment period. The diet for all animals, on a dry matter basis, contained 16 % crude protein. Potable water was available ad libitum. Pens were randomly distributed among the treatments:

TABLE 5

Trial	Treatment	Pens	Animals	Description
2	1	12	60	Control
2	2	12	60	80 mg/wk A-bST Subcutaneous
2	3	12	60	80 mg/wk A-bST Intraperitoneal
3	1	12	60	Control
3	2	12	60	80 mg/wk bST SQ Pellet

Trial	Treatment	Pens	Animals	Description
3	3	12	60	80 mg/wk bST IP Pellet
4	1	12	60	Control
4	2	12	60	80 mg/wk A-bST SQ Pellet
4	3	12	60	80 mg/wk A-bST 5P Pellet

The animals were slaughtered for carcass analysis. The results are shown in the following Tables:

TABLE 6

TREATMENT

Parameters	Control	80 mg/wk SQ bST Pellets	80 mg/wk IP bST Pellets
Carcass Wt. (kg)	395.1	395.0	397.7
Final Body Wt (kg)	493.7a	499.5a	507.8a
Carcass Wt. (kg)	304.2	304.2a	311.2a
Dressing Percent	61.6a	60.8~	61.2ab
Carcass Gain	--	0-	61~

Response			
Non-Carcass Gain Response	--	100-	39~

a, b - different superscripts indicate that numbers in a row significantly different ($p<.05$)

It can be seen that, while the dressing percentage of subcutaneously-treated cattle was significantly decreased relative to the control, the dressing percentage of intraperitoneally-treated was not significantly changed relative to the control.

Example 3b - Combination of Intraperitoneal bST Osmotic Pump and Estrogen Pellets

A study was undertaken to determine whether the effects of intraperitoneal release of bST, of estrogen pellets, or of the combined effects of the two.

Two hundred fifty-six cross-bred large frame steers weighing approximately 430 kg (lb) were assigned to a control group and three treatment groups and implanted with intraperitoneal bST pumps or/and estrogen pellets. The bST formulation used was a 35% An bST load in a phosphate buffer, glycerol, Tween-80 and KCl excipinet. The w/w/w% proportions respectively were 48.38/48.38/0.24/0%. The phosphate buffer was 60:40 monobasic:dibacsic sodium phosphate at 1.0M. The time of release of both bST and estrogen was 87 days prior to slaughter. The results are shown in the following Table.

TABLE 7

TREATMENT

			12mg/d		12mg/d
			12mg/d hST 0	0 bST/200ug/d	
	bST//200ug/d				
	Parameters	Control	Estrogen	Estrogen	Estrogen
	Initial Body Wt (kg)	430.3	430.3	430.3	430.3
	Final Body Wt (kg)	544.9a	552.2b	567.1c	576.4d
	Carcass Wt (kg)	334.2a	340.3b	349.3c	359.7d
	Parameters	Control	Estrogen	Estrogen	Estrogen
	Dressing Percent (%)	61.3a	61.6a	61.6a	62.4b
	Carcass Gain Response	N/A	84%	68%	112%
	Non Carcass Gain Response	N/A	16%	32%	-12%

a,b different superscripts indicate that number in a row are significantly different (P<.05) [what about c and d]

These results indicated that a significant improvement in dressing percentage and carcass weight were achieved by intraperitoneal osmotic pump release of bST concurrent with estrogen treatment.

Example 3c - Combination of Intraperitoneal bST Osmotic Pump and Estrogen Pellet

A study was undertaken to determine performance of intraperitoneal osmotic pumps in finishing cattle concurrently being administered estrogen. Six hundred seventy-two cross-bred large frame cattle weighing approximately 412 kg were bought and assigned to a control group and six treatment groups of 96 cattle each. The cattle were implanted with intraperitoneal osmotic pumps capable of delivering 6, 12, 15 or 18 mg bST per day during an 84-day period ending with slaughter. The cattle received estrogen pellets during a 126-day period ending with slaughter. The estrogen release is estimated at about 200 ug/d. The results are shown in the following table.

TABLE 8

	TREATMENT						
load		30%		40%	45%		
Parameters	Control	6μ /d	12μ/d	6μ /d	12μg/d	15μg/d	18μg/d
Initial Body Wt (kg)	411.9	411.9	411.9	411.9	411.9	411.9	411.9
Final Body Wt (kg)	555.1	565.6	568.7	561.8	563.5	569.6	566.5
Carcass Wt	343.0a	353.1bc	357.2d	355.4b	350.8b	351.3	353.8bcd

(kg)			8			
Dressing 62.5b Percent	61.8a	62.4b	62.8b	62.4b	62.4b	62.4b
Carcass 95% Response	---	96%	104%	84%	116%	99%
Non-Carcass Response 5%	--	4%	-9%	14%	-16%	1%

The results confirm that concurrent intraperitoneal treatment of finishing beef cattle with bST and estradiol significantly increase dressing percentage and carcass weight and furthermore allocated most of the increased weight to the carcass components.

The novel devices of this invention use means for the obtainment of precise release rates in a fluid environment of use while simultaneously maintaining the integrity of the device and the stability of the fluid-sensitive beneficial agent 7 within the device. While there has been described and pointed out features of the invention as applied to presently preferred embodiments, those skilled in the art will appreciate that various modifications, changes, additions and omissions in the

devices illustrated and described can be made without departing from the spirit of the invention.

WHAT IS CLAIMED IS:

1. A delivery device for storing and protecting a beneficial agent formulation and for dispensing the beneficial agent formulation to an animal, the delivery device comprising:

a) a housing comprising a first wall section and a second wall sections having ends assembled together in mated contact to form an internal compartment, wherein the first wall section is substantially impermeable to the passage of fluid, wherein the second wall section is permeable in at least a portion to the passage of fluid;

b) a beneficial agent formulation in a portion of the internal compartment comprised by the first wall section;

c) expandable means in a portion of the compartment comprised by the second wall section for pushing the beneficial agent formulation from the delivery device;

d) a partition layer substantially impermeable to fluid, the partition layer disposed between the beneficial agent formulation and the expandable means, wherein the partition layer includes a body portion and biasing means for slidably engaging the first wall section, the body portion adapted to be slidably received within the first wall section and the biasing means extending outward from the body portion to slidably engage the first wall section; and

e) exit means in the housing for delivering the beneficial agent formulation from the first section of the delivery device to the animal over a prolonged period of time.

2. A delivery device according to claim 1 wherein the biasing means includes a conical skirt extending outwardly from the body portion to slidably engage with the first wall section.

3. A delivery device for storing and protecting a beneficial agent formulation and for dispensing the beneficial agent formulation to an animal, the delivery device comprising:

a) a housing comprising a first wall section, a second wall section , and an enclosure means for enclosing the first wall section, the first wall section, the second wall section and the enclosure means assembled together to form an internal compartment, wherein the first wall section and the enclosure means are substantially impermeable to the passage of fluid, wherein the second wall section is permeable in at least a portion to the passage of fluid;

b) a beneficial agent formulation in a portion of the internal compartment comprised by the first wall section;

c) expandable means in a portion of the compartment comprised by the second wall section for pushing the beneficial agent formulation from the delivery device; and

e) exit means for delivering the beneficial agent formulation from the first section of the delivery device to the animal over a prolonged period of time, the enclosure means defining the exit means.

4. A delivery device according to claim 3 wherein the enclosure means includes an end cap, the end cap comprising an inwardly extending portion, the inwardly extending portion and the first wall section defining a space therebetween.

5. A delivery device according to claim 4, further including means for maintaining a seal between the exterior environment and the interior chamber until the osmotic pressure within the device reaches a predetermined pressure of between greater than 5 and 10 psi.

6. A delivery device according to claim 3, wherein the end cap includes mating means for adapting the end cap to ultrasonic welding to the first wall section, the mating means positioned where the end cap and the second wall section join.

7. A delivery device as set forth in claim 6, wherein end cap further comprises a first side and a second side, and wherein the mating means includes a tenon extending outwards from the second side of the end cap, the first wall section defining a mortise therein, the tenon sized and positioned for receipt within the mortise.

8. A delivery device according to claim 3 which further comprises a partition layer substantially impermeable to fluid between the beneficial agent formulation and the expandable means, wherein the partition layer includes a body portion and biasing means for slidably engaging the first wall section, the body portion adapted to be slidably received within the first wall section and the biasing means extending outward from the body portion to slidably engage the first wall section.

9. A delivery device according to claim 8 wherein the biasing means includes a conical skirt extending outwardly from the body portion to slidably engage with the first wall section.

10. A delivery device as set forth in claim 3, wherein the first wall section includes a first wall exterior surface, and wherein the second wall includes a second wall exterior surface, a second wall first end and a

second wall second end, the second wall first end for engagement with the first wall portion, the second wall first end including an end portion having an outer diameter sufficiently smaller that the inside diameter of the first wall portion such that the second wall end portion fits within the first wall section, defines an adhesive receiving space therebetween, and forms an abrupt transition from the first wall exterior surface to the second wall exterior surface, and wherein the delivery device further includes means for abutting the first wall section with the second wall section and smoothing the abrupt transition from the first wall section to the second wall section.

11. A delivery device according to claim 10, wherein the means for abutting with the first wall section and smoothing the transition from the first wall section to the second wall section comprises a buttress formed upon the second wall section and positioned to abut the first wall section.

12. A delivery device for storing and protecting a beneficial agent formulation and for dispensing the beneficial agent formulation to an animal, the delivery device comprising:

a) a housing comprising a first wall section and a second wall section having ends assembled together in mated contact to form an internal compartment, wherein the first wall section has a first wall section first end, a first wall section second end, and is substantially impermeable to the passage of fluid and wherein the second wall section has a second wall section first end, a second wall section second end, and is permeable in at least a portion to the passage of fluid, the second wall section second end engaged with the first wall portion, the second wall section second end having a portion having an outer diameter sufficiently smaller that the inside diameter of the first wall portion such that the second

wall portion fits within the first wall portion, defines an adhesive receiving space therebetween and forms an abrupt transition from the first wall section exterior surface to the second wall section exterior surface;

b) means for abutting the first wall section with the second wall section and smoothing the transition from the first wall section exterior surface to the second wall section exterior surface;

c) a beneficial agent formulation in a portion of the internal compartment comprised by the first wall section;

d) expandable means in a portion of the compartment comprised by the second wall section for pushing the beneficial agent formulation from the delivery device; and

e) exit means in the end cap for delivering the beneficial agent formulation from the first section of the delivery device to the animal over a prolonged period of time.

13. A delivery device according to claim 12, wherein the means for abutting with the first wall section and smoothing the transition from the first wall section to the second wall section includes a buttress formed upon the second wall section and positioned to abut the first wall section.

14. A delivery device according to claim 13 wherein the means for abutting the first wall section with the second wall section and smoothing the transition from the first wall to the second wall includes the first wall section having a first wall section inner diameter and an annular interior ledge, the first wall inner diameter sized to receive the second wall section snugly therein, and the second wall section having a second wall section outer diameter sized to fit within the first wall section, the first wall section and the second wall section defining an adhesive receiving space therebetween; and a buttress, the buttress

formed on the second wall section and positioned to abut with the first wall section when the first wall section is joined with the second wall section to form the internal compartment and the second wall section is abutted with the annular interior ledge.

15. A delivery device according to claim 12 which further comprises a partition layer substantially impermeable to fluid between the beneficial agent formulation and the expandable means, wherein the partition layer includes a body portion and biasing means for slidably engaging the first wall section, the body portion adapted to be slidably received within the first wall section and the biasing means extending outward from the body portion to slidably engage the first wall section.

16. A delivery device according to claim 14 wherein the biasing means includes a conical skirt extending outwardly from the body portion to slidably engage with the first wall section.

17. A delivery device for storing and protecting a beneficial agent formulation comprising bovine somatotropin or an analogue or derivative thereof and for dispensing the beneficial agent formulation to a bovine animal, the delivery device comprising:

a) a housing comprising a first wall section and a second wall section assembled together in mated contact to form an internal compartment, wherein the first wall section is substantially impermeable to the passage of fluid, and wherein the second wall section is permeable in at least a portion to the passage of fluid;

b) a beneficial agent formulation comprising bovine somatotropin or an analogue or a derivative thereof in a portion of the compartment comprised by the first wall section, wherein said

first wall section further includes means for reducing the adherence of the beneficial agent formulation to the first wall section;

c) expandable means in a portion of the compartment comprised by the second wall section for pushing the beneficial agent formulation from the delivery device; and

d) exit means in the first wall section for delivering the beneficial agent formulation from the delivery device to the bovine animal.

18. A delivery device according to claim 16 wherein said means for reducing adherence includes forming the first wall section of a material which reduces the adherence of the beneficial agent to the first wall section.

19. A delivery device according to claim 17, wherein the material includes polypropylene.

20. A delivery device for storing and protecting a beneficial agent formulation and for dispensing the beneficial agent formulation to an animal, the delivery device comprising:

a) a housing comprising a first wall section, a second wall section, and an end cap, the first wall section, the second wall section and the end cap assembled together to form an internal compartment, wherein the first wall section and the end cap are substantially impermeable to the passage of fluid and, wherein the second wall section is permeable in at least a portion to the passage of fluid;

b) means for abutting the first wall section with the second wall section;

b) a beneficial agent formulation in a portion of the internal compartment comprised by the first wall section and the end cap;

c) expandable means in a portion of the compartment comprised by the second wall section for pushing the beneficial agent formulation from the delivery device;

d) a partition layer substantially impermeable to fluid, the partition layer between the beneficial agent formulation and the expandable means, wherein the partition layer includes a body portion and biasing means for slidably engaging the first wall section, the body portion adapted to be slidably received within the first wall section and the biasing means extending outward from the body portion to slidably engage the first wall section; and

e) exit means in the end cap for delivering the beneficial agent formulation from the delivery device to the animal.

21. A delivery device according to claim 19 wherein the enclosure means includes an end cap, the end cap comprising an inwardly extending portion, the inwardly extending portion and the first wall section defining a space therebetween.

22. A delivery device according to claim 20, wherein the end cap further includes mating means for adapting the end cap to ultrasonic welding to the first wall section, the mating means positioned where the end cap and the second wall section join.

23. A delivery device as set forth in claim 21, wherein the mating means includes a tenon extending outwards from the end cap, the second wall section defining a mortise therein, the tenon sized and positioned for receipt within the mortise.

24. A delivery device according to claim 19, wherein the means for abutting with the first wall section includes a buttress formed upon the second wall section and positioned to abut the first wall section.

25. A delivery device for storing and protecting a beneficial agent formulation and for minimizing the dilution of the beneficial agent formulation during the dispensing of the beneficial agent to an animal, the delivery device comprising:

a) a housing comprising a first wall section and a second wall section assembled together to form an internal compartment, wherein the first wall section is substantially impermeable to the passage of fluid, wherein the second wall section is permeable in at least a portion, to the predetermined rate of fluid from the external environment into internal compartment comprised by the second wall section;

b) a beneficial agent formulation in a portion of the compartment comprised by the first wall section;

c) expandable means in a portion of the compartment comprised by the second wall section for pushing the beneficial agent formulation from the delivery device; and

d) exit means in the first wall section for maintaining sufficient outward velocity of the beneficial agent formulation from the delivery device to the bovine animal to prevent an inward flow of fluid from the external environment to dilute the beneficial agent formulation in the portion of the compartment comprised by the first wall section.

26. A delivery device according to claim 25, the wherein the beneficial agent is bovine somatotrophin and the predetermined rate of

fluid from the external environment is about 10 to about 15 mg/water per day.

27. A delivery device according to claim 26, wherein the predetermined rate of fluid is attained by a selected thickness of the second wall section, a selected surface area of the second wall section, and second wall section comprising a selected material.

28. A device according to claim 27, wherein the exit means further includes the first wall section defining a passageway of a predetermined inner diameter sufficient to generate a sufficient outward velocity of the the beneficial agent formulation to prevent an inward flow of fluid from the external environment to dilute the beneficial agent in the portion of the compartment comprised by the first wall section.

29. A device according to claim 28 wherein the exit means further includes means for compensating for slight variations in the outward flow rate.

30. A device according to claim 29 wherein the means for compensating for slight vairiaiations in the outward flow rate includes adjusting the thickness of the first wall section defining the exit means therein.

31. A delivery device for storing and protecting a beneficial agent formulation and for minimizing the dilution of the beneficial agent formulation during the dispensing of the beneficial agent to an animal, the delivery device comprising:

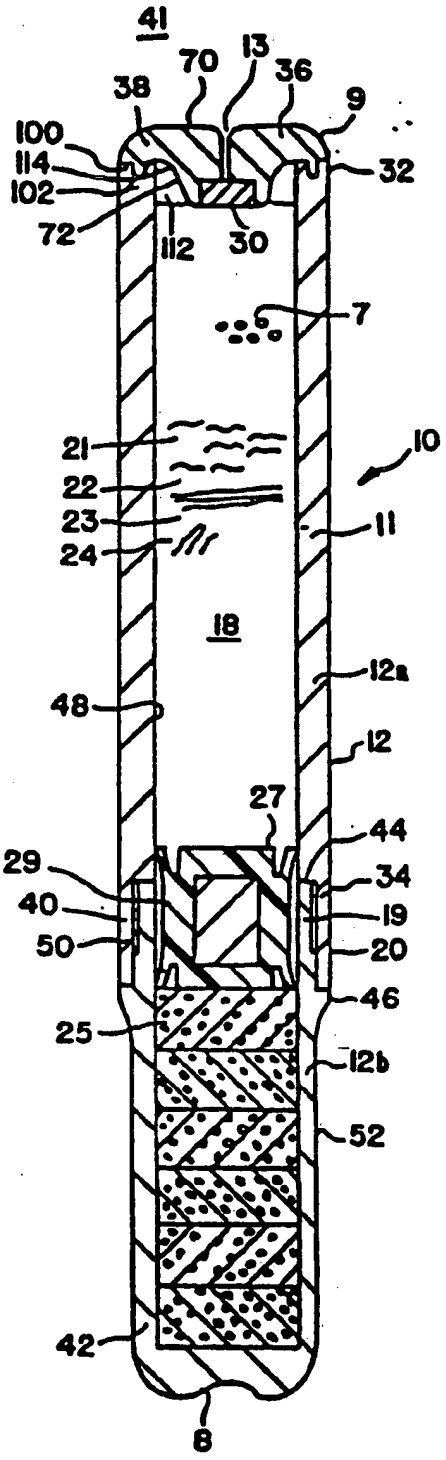
a) a housing comprising a first wall section and a second wall section assembled together to form an internal compartment,

wherein the first wall section is substantially impermeable to the passage of fluid, wherein the second wall section comprises cellulose acetate butyrate, permeable in at least a portion, to a rate of fluid of about 12-14 mg/day from the external environment into internal compartment comprised by the second wall section;

b) a beneficial agent formulation comprising bovine somatotrophin in a portion of the compartment comprised by the first wall section;

c) expandable means in a portion of the compartment comprised by the second wall section for pushing the beneficial agent formulation from the delivery device; and

d) exit means in the first wall section for maintaining sufficient outward velocity of the beneficial agent formulation from the delivery device to the bovine animal to prevent an inward flow of fluid from the external environment to dilute the beneficial agent formulation in the portion of the compartment comprised by the first wall section, the exit means further including a exit passageway of about 0.100 inches in length and having an diameter of about 0.017 inches .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10
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46
25
12b
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42
8

FIG. 1

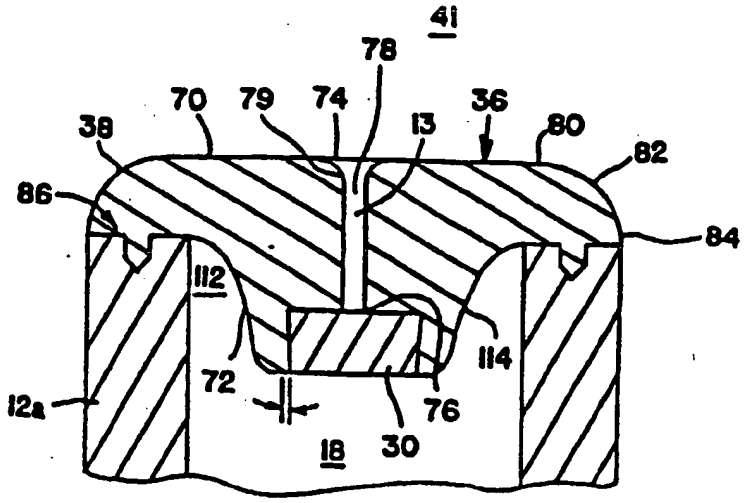


FIG. 2

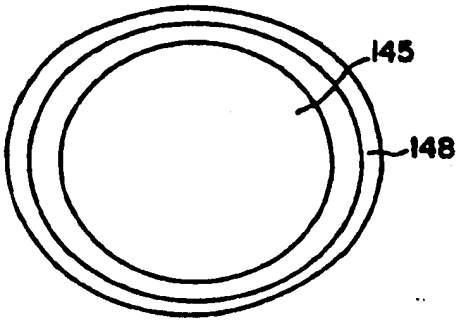


FIG. 7

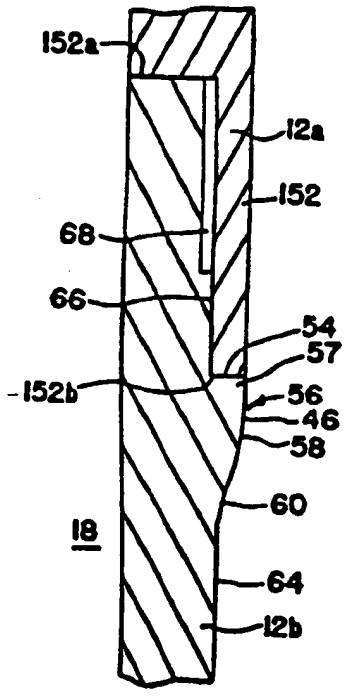


FIG. 5

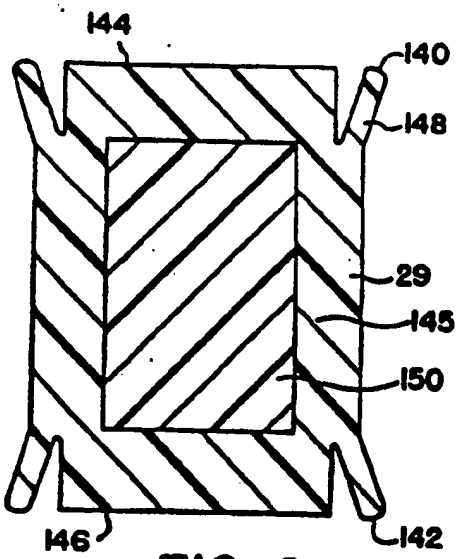
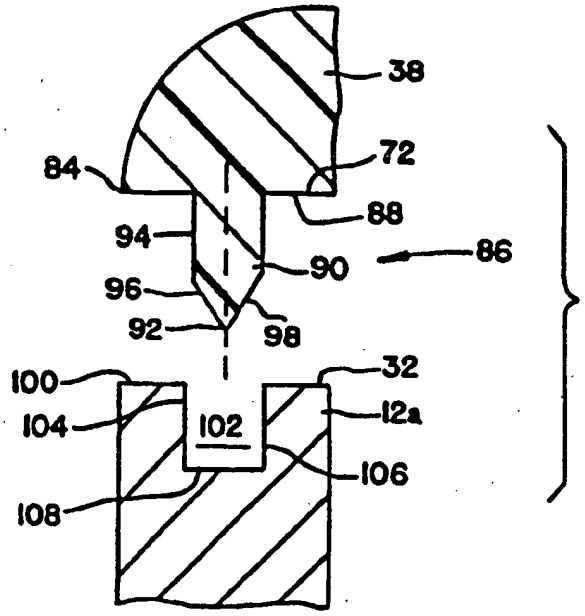


FIG. 6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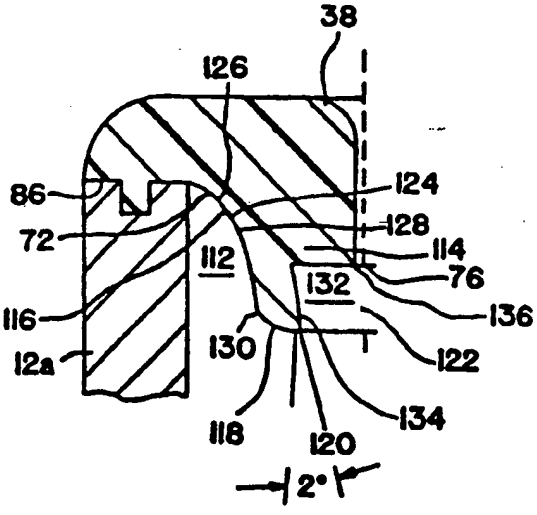
102
12a
106
108

FIG. 3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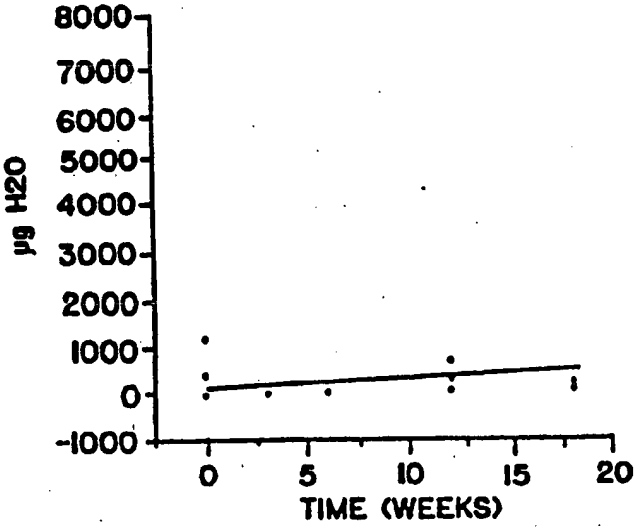
2°

FIG. 4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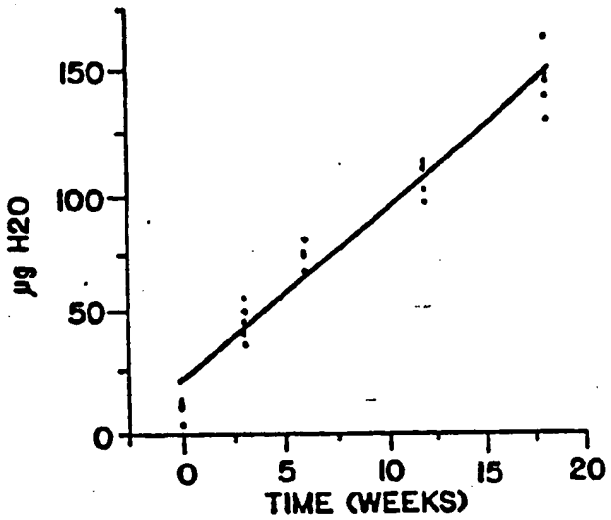
7000
6000
5000
4000
3000
2000
1000
0
-1000
µg H20
0
5
10
15
20
TIME (WEEKS)

FIG. 8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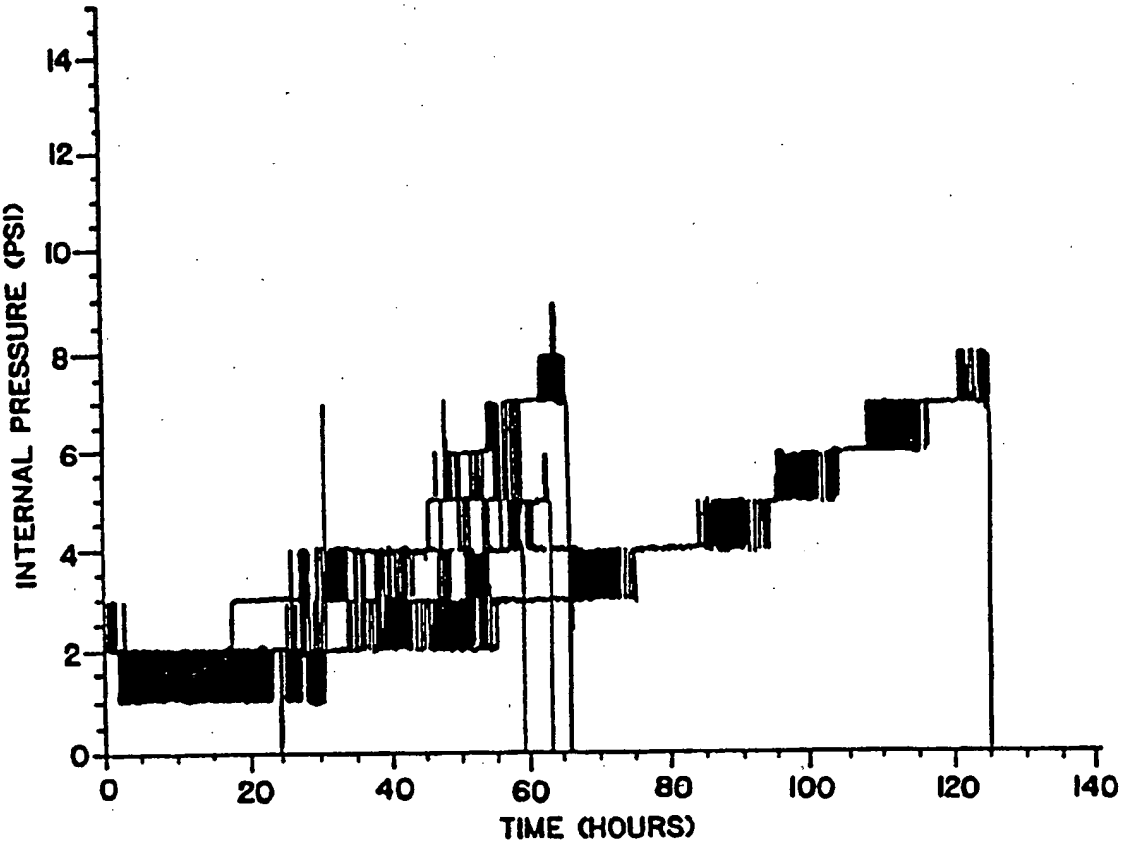
50
0
µg H20
0
5
10
15
20
TIME (WEEKS)

FIG. 9

84

5/6


INTERNAL PRESSURE (PSI)
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2
4
6
8
10
12
14
0
20
40
60
80
100
120
140
TIME (HOURS)

FIG. 10

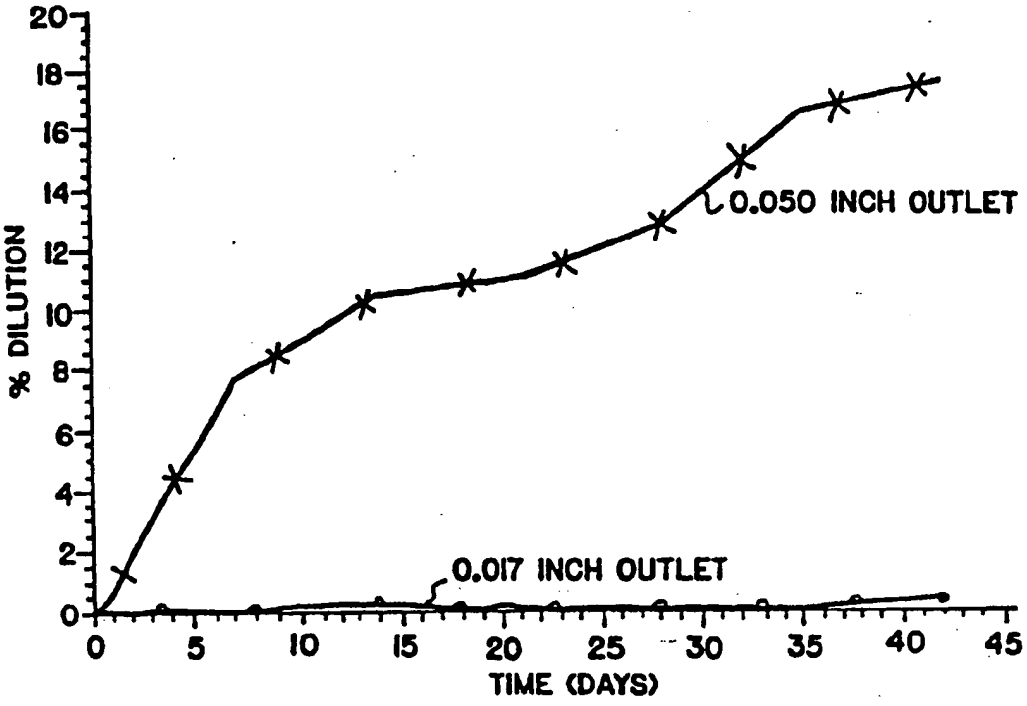
20
18
16
14
12
10
8
6
4
2
0
% DILUTION
0.050 INCH OUTLET
0.017 INCH OUTLET
0
5
10
15
20
25
30
35
40
45
TIME (DAYS)

FIG. 11

APPENDIX B

INCREASING DRESSING PERCENTAGE AND CARCASS WEIGHT IN FINISHING BEEF CATTLE

FIELD OF THE INVENTION

The invention relates to the treatment of beef cattle during the finishing stage of growth. In a particular aspect the invention relates to treating beef cattle during the finishing stage of growth in a feed lot to increase weight gain and to increase the proportion of weight gain which appears in carcass components, significantly increasing both dressing percentage and carcass weight.

BACKGROUND OF THE INVENTION

Bovine somatotropin (bST), usually in the form of recombinant bST (rbST), is a broad-acting polypeptide hormone which influences a wide range of complex functions in cattle, including growth rate, maturation, milk production and the like.

Studies on the use of bST in finishing beef cattle to provide commercially advantageous methods of preparing beef cattle for slaughter have successfully increased the average daily gain and slaughter weight of the cattle. However, bST treatment typically decreases the dressing percentage of the cattle.

When cattle are slaughtered, the body weight consists of carcass weight, non-carcass body components, and digestive fill. The carcass weight is the weight of the carcass, including the kidneys, but not including the head, hide, hooves, viscera including digestive fill, and other internal organs. The ratio of the carcass weight of the animal to the total body weight in percent is referred to as the dressing percentage.

bST administration to beef cattle during the finishing stage of growth has also been found, when continued substantially until slaughter, to increase the proportion of weight gain which appears in non-carcass components. This calculation can frequently be made

from data presented in the prior art references. Thus, bST-induced increase in body weight has typically been disproportionately allocated to commercially less-valuable non-carcass components of the animals.

When cattle are being prepared for slaughter, it would be advantageous to increase significantly both the dressing percentage and the carcass weight, since in this way the investment in feed supplementation and treatment during the finishing stage would reduce cost per unit of meat. Heretofore, there has been no reliable method of significantly increasing the dressing percentage of cattle receiving bST and preferentially allocating the increase in body weight to the more valuable carcass components.

Fabry et al., "Influence de l'hormone de croissance sur la production de viande chez les genisses," Reprod. Nutr. Develop. Vol. 27 (2B) 591-600 (1987) showed that the dressing percent value in heifers of the Belgian White Blue breed injected daily with about 50 milligram/day (mg/d) of bST dropped from 58.9% to 57.9%. Only about 36% of the weight increase in the bST-treated heifers appeared in the carcass components.

Early et al., "Growth and Metabolism in Somatotropin-treated Steers: I. Growth, Serum Chemistry and Carcass Weights," J. Anim. Sci. 68:4134-4143 (1990) showed that the dressing percent value in Hereford steers daily injected with about 20 mg/d of bST dropped from 53.8% to 51.8%. Early et al., Growth and Metabolism in Somatotropin-treated Steers: II. Carcass and Noncarcass Components and Chemical Composition," J. Anim. Sci. 68:4144-4152 (1990) showed that most of the body weight gain in such steers was in the non-carcass components. Only about 12% of the weight increase in the bST-treated steers appeared in the carcass components.

Mosely et al., "Recombinant Bovine Somatotropin Improves Growth Performance in Finishing Beef Steers," J. Anim. Sci. 70: 412-425 (1992) showed in two experiments that increasing dosage of bST administered by daily injection to cross-bred steers in the finishing stage of growth, while increasing feed efficiency ("FE") and average daily gain ("ADG"), decreased dressing percentage. In a first experiment, dosages of rbST of 33 and 100 ug/kg decreased dressing percentage from 62.7 to 61.3% and a dosage of 300 ug/kg decreased dressing percentage from 62.7 to 58.7%. In a second experiment, treatment with rbST at 8.25, 16.5, or 33 ug/kg decreased dressing percentage from 63.2 to 62.5 or 62.6% while treatment with 66 ug/kg rbST reduced dressing percentage from 63.2 to 61.9%. The cattle were slaughtered at constant weight. These studies suggested that as average daily bST dose increased, the extent to which dressing percent was diminished also increased.

Wagner et al., "Effect of growth hormone (GH) and estradiol ($E_2\beta$) alone and in combination on beef steer growth performance, carcass and plasma components," showed that subcutaneous injections of a biweekly-administered oil formulation containing 960 mg bST to cross-bred beef steers decreased dressing percent from 63.0% to 61.1%. In combination with estradiol, rbST treatment decreased dressing percentage from 64 to 61.4%. The biweekly bST treatment, in the presence or absence of estradiol, resulted in all of the weight increase being allocated to the non-carcass components.

In Enright et al., Effects of long term administration of pituitary-derived bovine growth and estradiol on Friesian steers, J. Anim. Sci. 68: 2345-2356 (1990), daily injections of bST were discontinued at 22 weeks whereas estradiol treatment was continued until slaughter at 30 weeks. Carcass analysis was not obtained at the end of bST administration, but was

conducted eight weeks after the last bST injection. Sandles et al., Anim. Prod. 44:21-27 (1987) had shown that bST effects were lost about 5 weeks after cessation of bST injection. Thus, carcass data obtained eight weeks post bST injection may not be valid for examining bST dressing percentage responses. bST administration to the finishing stage cattle ending eight weeks prior to slaughter generally had no significant effect on carcass weight and had no significant effect on dressing percentage.

Preston et al., "Comparative effects of BST and steroidal growth promotants in feedlot steers," American Society of Animal Science, American Dairy Science Association, Midwest Section, March 23-25, 1992, reported that when bST was administered by intraperitoneal sustained release pellets (first-order release) dressing percent was not significantly changed. See, also, Preston et al., "Role of protein level and source on the response of feedlot steers to levels of somatotropin," Journal of Animal Science, Volume 71, Supplement 1, Abstract 173.

Rumsey et al., Growth Response to an estrogenic growth promoter and recombinant bovine somatotropin (bST) in young beef steers, FASEB 1994 pA158, Abstract Number 917 reported results of treating young cross-bred steers with bST, estrogen, and a combination of bST and estrogen. Rumsey et al. did not report dressing percentage, but provided data from which the dressing percentage for the various treatments could be estimated. These data indicated that treatment with estradiol increased dressing percent (57%), that bST treatment decreased dressing percent (53%) and that concurrent treatment with bST and estrogen/progesterone resulted in no change in dressing percent (54%), all relative to controls (54%).

In McBride and Mosely, Influence of Exogenous Somatotropin on the Components of Growth in Ruminants, the authors summarize the work on bST in cattle and sheep: Body weight gain is often accompanied by an increase in non-carcass components and the carcass weight may not be significantly increased.

Thus, summarizing these articles, while estrogen alone had been observed to increase dressing percentage in cattle not being treated with bST, there remains a need for an effective treatment which includes administration of bST and which will significantly increase both dressing percentage and carcass weight of cattle in the finishing stage of growth.

These and other advantages can be achieved by those skilled in the art in accordance with the invention herein disclosed. The invention is not limited to the embodiments specifically disclosed herein, but by the claims attached hereto interpreted in accordance with law.

SUMMARY OF THE INVENTION

It has been discovered that treatment of cattle in the finishing stage of growth with intraperitoneally released bST, concurrent with treatment by an estrogenic agent, increases the proportion of gained weight which appears in the carcass components. That is, treatment of beef cattle in the finishing stage of growth in accordance with the invention increases the relative proportion of weight of the carcass components and decreases the relative proportion of weight of the non-carcass components.

The invention comprises a method of preparing beef cattle for slaughter. A source of bST is implanted in the intraperitoneal space of beef cattle in the finishing stage of growth being prepared for slaughter. bST is released in the intraperitoneal space at a rate

and a dose effective for increasing the body weight (BW) or feed conversion efficiency (FE) or carcass weight (CW) or average daily gain (ADG) of beef cattle in the finishing stage of growth over an extended period of time ending substantially at slaughter of the animals. Concurrently, the animals are treated subcutaneously or intraperitoneally with an estrogenic agent at a dose effective for increasing the body or carcass weight (BW or CW) of beef cattle in the finishing stage of growth. The dressing percentage and carcass weight of the bST- and estrogenic agent-treated animals are significantly increased.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to a method of preparing beef cattle in the finishing stage of growth for slaughter. The finishing stage of growth is the final stage of growth before slaughter, and follows the stocker stage of growth when the bovine receives nutrients primarily from pasturage or hay, optionally with feed supplementation, which in turn follows the calf or suckling stage when the calf receives nutrients primarily from its mother.

Cattle in the finishing stage of growth are generally nonlactating bovines (steers or heifers) of 12 months (or even as low as 3 months) to 2 years of age who are undergoing rapid growth. The finishing stage of growth can be regarded as beginning when the typical beef stocker is about 700 pounds (about 320 kg) of weight. Such animals will usually be slaughtered when a weight of about 1000 or 1300 pounds (about 450 kg or 600 kg) or more is reached.

The finishing stage of growth is a period of time during growth when the bovine is of sufficient size and age when supplied with a suitable feed to undergo a rapid average daily weight gain, for example, an average

daily gain of at least 1 kg/d, that is, when the rate of weight gain is 1 or more than 1 kg/d. Typically, cattle during this phase of growth can gain in the range of about 1 to about 2 kilograms or even more per day. Preferably, the cattle treated in accordance with the invention are high-performance cattle capable of growth at a rate of greater than about 1.5 kg/d, most preferably at a rate greater than about 1.7 kg/d. The current limit of average daily gain (ADG) during finishing is about 3 kg/d; however, as higher performance cattle are developed, this limit may be exceeded. In any case, the range above 1 or 1.5 etc. kg/d is finite and definite and will be known to those skilled in the art.

During the finishing stage of growth, the bovine feed may be supplemented with concentrated feed, richer than pasturage or hay in digestible proteins, carbohydrates, and fats. Typically, during the finishing stages, feed grain may constitute from 12 to 80% or more of the animal's feed. The feed may contain from 12 to 16 percent or more protein or protein-equivalent nitrogen. National Research Council. (NRC) guidelines permit finishing at as low as 9% protein - equivalent nitrogen.

It has been found that feed efficiency, body and carcass weight and dressing percent are advantageously influenced when beef cattle receiving an estrogenic agent are treated intraperitoneally with an effective dose and rate of release of bST during this period of growth.

bST (bovine somatotropin) refers to any protein having bovine somatotropin activity. The bovine somatotropin can be pituitary-derived or recombinantly produced bovine somatotropin. The bST can be a naturally-occurring sequence or a sequence altered by addition or deletion or substitution of one or more

amino acids. All of these forms of bovine somatotropin are now well-known to those skilled in the art.

Examples of bovine somatotropin variants include, but are not limited to, polypeptides having the following amino acid sequences with unspecified amino acid residues being the same as or similar to the naturally occurring somatotropin:

NH_2-met-phe(1)-pro(2)....leu(126)....phe(190)-COOH

NH_2-met-phe(1)-pro(2)....val(126)....phe(190)-COOH

NH_2-ala-phe(1)-pro(2)....val(126)....phe(190)-COOH

NH_2-ala-phe(1)-pro(2)....leu(126)....phe(190)-COOH

NH_2-phe(1)-pro(2)....leu(126)....phe(190)-COOH

NH_2-phe(1)-pro(2)....val(126)....phe(190)-COOH

NH_2-met-asp-glu-phe(1)-pro(2)....leu(126)....phe(190)-COOH

NH_2-met-asp-glu-phe(1)-pro(2)....val(126)....phe(190)-COOH

NH_2-met(4)-ser(5)....leu(126)....phe(190)-COOH

NH_2-met(4)-ser(5)....val(126)....phe(190)-COOH

NH_2-met-phe(10)....leu(126)....phe(190)-COOH

NH_2-met-phe(10)....val(126)....phe(190)-COOH

The first variant in the list above, with a methionyl residue at the N-terminus, and a leucyl residue at position 126 may be specifically referred to as methionyl bovine somatotropin or "MBS", and the third variant in the list above, with an alanyl residue at the N-terminus and a valyl residue at position 126 may be referred to as alanyl-valyl bovine somatotropin or "ala-val BST" or "A-BST". Metal complexes of such bST, such as zinc and copper complexes, may also be used and are referred to as Zn-bST or Cu-bST. See, e.g., U.S. Patent 4,863,736.

It is understood that the additional N-terminal methionyl residue on the variants described above could also be removed, either during or after expression. It is also understood that one or more amino acids of the following sequence -glu-arg-ala-tyr-ile-pro-glu- (which

are numbers 32-38 of the bovine somatotropin sequence set forth above) may be deleted. This type of deletion is described in European Patent Application, Publication Numbers 282,318, and 282,319, both of which were published September 14, 1988. Other deletion variants with somatotropin activity can also be used, such as deletion of amino acids 32-45.

The somatotropins found most effective for administration via the composition of the invention are those which have an N-terminal group of methionine and are associated with zinc metal. See, e.g., U.S. Patent B1 4,985,404, incorporated herein by reference.

The formulation of bovine somatotropin for use in an osmotic implant may generally include a stabilizing polyol. The phrase "stabilizing polyol" means polyol, for example, with three hydroxyl groups, which maintains the somatotropin in a physically stable composition, i.e. the somatotropin does not precipitate to an undesirable degree over reasonable storage or administration period. Glycerol is the preferred polyol, however, other polyols may be used, such as tris(hydroxymethyl)aminomethane.

The formulation may further include a physiologically compatible buffer, incorporated for maintaining the pH exhibited by the composition within a range in which the somatotropin is bioactive. Generally, the pH exhibited by the solution should be between a minimum of about 4.5 or, preferably about 5, or more preferably 5.7 and a maximum of the greater of about 7 and about the isoelectric point of the somatotropin. The isoelectric point for A-BST is 8.6. These isoelectric points are for the standard monomeric forms obtained in bulk preparation of these somatotropins. Isoelectric points for other variants, other derivatives and other forms can be determined using standard techniques. For A-BST, the optimum pH is

about between about 6.1 and about 7.5. Although various buffers can be used, it is preferred that the buffer be an alkali metal phosphate. To provide buffering in the desired pH range, it is particularly preferable that the buffer be comprised substantially of monobasic:dibasic phosphates such as, for example, mono-or-di-sodium or potassium phosphates at 1M or 0.45 M or the like. Another effective buffer for controlling the pH in the desired range is a histidine hydrohalide such as histidine hydrochloride. Additional buffers that maintain this pH range are citrate buffers and acid addition salts of tris(hydroxymethyl)aminomethane, such as the hydrochloride salt. These tris(hydroxymethyl)aminomethane salts also contain hydroxyl groups and can act as a stabilizing polyol in some circumstances. Any other buffer that can maintain a pH in the desired range can be used.

It should incidentally be noted that direct measurement of the pH of the composition of the invention may not in all instances be practical. To provide a practical measurement, however, a small quantity such as a drop of the composition may be placed in about 10 ml of water, and the pH of the resulting mixture determined. It is believed that the actual pH of the composition is closely approximated by this measurement, but, in any event, it will be understood that the pH measured at such dilution is considered for purposes of this disclosure to be the pH exhibited by the composition itself.

In order to promote wetting of the somatotropin by the buffer/polyol excipient during preparation of the formulation, a wetting agent, such as a nonionic surfactant is preferably incorporated as well. Such surfactant also inhibits foaming. The surfactant can be present in the excipient at amounts between about 0.005% and about 2.5% more preferably about 0.25%. A

particularly preferred nonionic surfactant is a polyethoxylated sorbitan ester, such as a tri(polyoxyethylene) ester of sorbitan mono-oleate, such as that sold under the trade designation Tween 80 by ICI Americas Inc.

An advantage of the use of a buffered polyol excipient for the somatotropin is the high loading achievable due to the high solubility of the somatotropin in the excipient liquid. Despite the high concentration of somatotropin in a composition which also contains a significant fraction of water, the pH maintained by the buffer inhibits the formation of dimers and other aggregates. Although it has not been determined whether the somatotropin is true solution or colloidal solution, it is desirable that the somatotropin does not precipitate or otherwise separate from the excipient, either on standing or under the influence of shear encountered in passage of the composition through the discharge opening of an infusion pump. The concentration of somatotropin in the composition is at least about 10% by weight, preferably at least about 15% by weight, more preferably at least about 20% by weight and even more preferably at least about 25% or even about 30% by weight. The somatotropin concentration may range as high as about 45% by weight. The polyol concentration may be at least about 20% by weight or 25% by weight and may range as high as 80% by weight or 70% by weight or 60% by weight or 50% by weight or 40% by weight. A relatively high glycerol content additionally provides a bacteriostatic effect. It is generally considered that an excipient containing about 50% glycerol provides bacteriostatic effect. The osmotic implant may further contain an estrogenic agent, for example, 17-β-estradiol, at a concentration of about .05 to about 1%, more preferably about 0.18 to about 0.72%.

Preferably, the formulation further comprises a wetting agent, such as nonionic surfactant with optimum concentrations between about 0.005% or about 2.5% by weight. Except for the buffer salt, which in the case of a phosphate buffer may typically comprise 4% to 7% by weight, and the sodium or potassium chloride which may be added to stabilize the formulation, described below, the balance of the formulation typically is water. A preferred formulation contains at least about 7% water, more preferably at least about 15% water, and even more preferably between about 25% and about 35% by weight water.

Optionally an alkaline halide such as sodium chloride or potassium chloride is added to the excipient prior to formulation with somatotropin. It has been found that this facilitates maintaining homogeneity of the formulation during filling of the implants, for example, when using Zn-bST. Following addition of the somatotropin to the excipient, the filled implant can be subjected to heat treatments from about 6 to 24 hours, preferably 16 hours, at a temperature between about 35°C and 50°C, preferably 39-46°C, most preferably about 40°C. Preferably the alkaline chloride comprises about 1 to about 4% by weight of the final formulation.

The formulation is normally a clear, homogeneous single phase. The formulation appears as a solid or semisolid at typical storage temperatures of about 4°C. The formulation decreases in viscosity to produce a viscous liquid at the body temperature of an animal. In this way, the formulation can be dispensable without being readily fluid at all temperatures.

As the concentration of somatotropin rises above 25%, the ratios of water and buffer to somatotropin preferably decline with increasing somatotropin concentration so as to maintain a polyol concentration as high as practicable. However, polyol content is

limited by viscosity considerations, and the maximum polyol concentration is about 40-45% for formulations having a hormone content about 25%. Higher polyol concentrations provide a benefit in physical stability, but can result in viscosity that makes handling difficult.

Preferably the bST is an aqueous suspension of bST formulated for release in an osmotic pump as hereinafter described. Such formulations can include glycerol, monobasic and dibasic sodium phosphate buffer, Tween-80, an alkaline halide salt such as sodium chloride and/or potassium chloride, but are not limited to these ingredients, in addition to the active ingredients such as bST and the estrogenic agent.

The currently preferred formulation comprises 36.5% ± 1.5% for Zn-bST in a phosphate buffer, glycerols, wetting agent, salt excipient blend where the w/w/w/w proportions of phosphate buffer, glycerol, Tween-80, and KCl are 48.38/48.38/0.24/3.0 respectively. The phosphate buffer is 60:40 monobasic:dibasic sodium phosphate, and the molarity is 0.45.

The preferred composition containing an estrogenic agent comprises about 0.06% to about 3.0% 17-beta-estradiol.

According to the invention, bST is intraperitoneally released in beef cattle in the finishing stages of growth at an effective dose and rate for significantly increasing a parameter selected from the group consisting of body weight (BW), carcass weight (CW), average daily gain (ADG) or feed efficiency (FE) of the animal. By significantly increasing is preferably meant that the dose is preferably effective at $P<.05$ which is a standard for demonstrating a beneficial effect.

The peritoneum is the serous membrane lining of the abdominal walls (parietal peritoneum) and investing the viscera (visceral peritoneum). The parietal peritoneum

is the membrane which lines the abdominal and pelvic walls and the undersurface of the diaphragm. The visceral peritoneum is the membrane reflected at various places over the viscera, forming a complete covering for the stomach, spleen, liver, ascending portion of the duodenum, jejunum, ileum, transverse colon, sigmoid flexure, upper end of the rectum, uterus, and ovaries; it also partially covers the descending and transverse portions of the duodenum, the cecum, ascending and descending colon, the middle part of the rectum, the posterior wall of the bladder, and the upper portion of the vagina. The peritoneum serves to hold the viscera in position by folds, some of which form the mesenteries, which connect portions of the intestine with the posterior abdominal wall; others, the omenta, folds attached to the stomach, and still others, the ligaments of the liver, spleen, stomach, kidneys, bladder, and uterus. The space between the parietal and visceral peritoneums is the Peritoneal Cavity, which consists of the Pelvic Peritoneal Cavity below and General Peritoneal Cavity above. The General Peritoneal Cavity communicates by the Foramen of Winslow with the Cavity of the Great Omentum, which is also known as the Lesser Peritoneal Cavity. As used herein, intraperitoneal cavity includes any of the Pelvic Peritoneal Cavity, the General Peritoneal Cavity, and the Lesser Peritoneal Cavity. More preferably, the implant is inserted into the Lesser Peritoneal Cavity. It has been established that access to the peritoneal cavity is best gained by inserting a trocar through the left paralumbar fossa. Initially, it was thought that insertion through the right paralumbar fossa would be the preferred side, as the rumen is positioned adjacent to the left paralumbar fossa. However, it was determined that the position of the kidneys and associated kidney are asymmetrically distributed toward

the right side of the body and interfere with trocar access to the peritoneal cavity. For this reason access to the peritoneal cavity is more easily accomplished through the left paralumbar fossa.

The implantation is preferably accomplished using a two step procedure. In the first step, a vertical incision is made substantially through the hide alone of the left paralumbar fossa. The incision is vertical relative to the ground and preferably less than 25mm or 20mm in length. In the second step, a sterile non-toxic plastic tube having, for example, a 30° bevel at the tip, optionally double-beveled, and providing a substantially-non-incising puncturing tip, is inserted through the incision and into the peritoneum. Sterile implants are inserted therethrough and the tube is removed and the wound permitted to close. Further description is provided in Appendix B hereto which is incorporated herein by reference.

The bST is intraperitoneally released since it has been observed that subcutaneous daily injections or prolonged non-intraperitoneal release can result in a decrease or in a nonsignificant change in dressing percentage and have not resulted in significant increases in dressing percentage and carcass weight.

Generally, it has been found that a practical minimum rate of release for observing significant changes in body weight or carcass weight or average daily gain or feed efficiency is about 3 mg/d bST and that above about 14 mg/d bST, there is little additional improvement. For advantageous results, the intraperitoneal daily release is maintained preferably in the range of about 3 mg/d to about 14 mg/d. However, higher dosages can also be employed. More preferably the intraperitoneal daily release is maintained in the range of about 6 or 9 to about 12 mg/d.

The release is preferably continuous since daily injections or biweekly injections can cause a reduction in dressing percentage. See, e.g., Mosley et al., op. cit., and Wright et al., op. cit. However, a pulsatile intraperitoneal release enhancing dressing percent is within the scope of the invention, for example, a pulsatile release 6, 12 or more times per day so that noncarcass growth is not unduly stimulated.

The preferably continuous release can be zero-order or non-zero order provided that the release threshold is preferably maintained in the range of above about 3 mg/d to about 14 mg/d, more preferably in the range of about 9 to about 12 mg/day that is, provided that the rate of release does not fall below a value in these ranges during substantially the entire period of treatment. Preferably, also, the rate of release does not exceed values of these ranges since higher dosages of bST which are not maintained over the long term may favor increase in weight of non-carcass organs and such higher dosages may result if a prolonged continuous intraperitoneal release above the minimum is to be achieved using a non-zero release implant.

bST is released at a substantially zero-order rate of release when the rate of release is substantially independent of the amount of bST remaining in the implant. It is preferred that the release be substantially zero-order. Thus, for example, a constant rate of release is zero-order. Such a rate of release can be accomplished by an osmotic implant such as described in Appendix A attached hereto and incorporated herein by reference.

Preferably the bST administration is effected by such an implantable device capable of delivering the desired dose of bST intraperitoneally for a prolonged period of time. Preferably, as indicated, the osmotic implant is such as is described in the patent

application attached hereto as Appendix A and incorporated herein by reference. Other methods of achieving a substantially zero-order rate of release can also be used, for example, a pellet of bST having an approximately constant-area release surface, or using other techniques known to those skilled in the art.

In the prior art, bST daily injection produced serum bST levels that were 400 to 700% higher than baseline for the first four hours post-injection and returned to baseline about 12 hours after injection (Enright et al., 1990 and Early et al., 1990a); whereas continuous bST delivery from a pellet has been found to produce about a 100% increase in serum bST in Holstein heifers and no detectable increase in serum bST in cross-bred steers. These data support a hypothesis, which should not be considered to limit the invention, that a less-variable more-continuous rate of delivery of bST in steers may reduce the disproportionate growth of non-carcass components by establishing an effective blood level for promoting growth of the carcass components that does not exaggerate the growth of viscera and other non-carcass components. Wagner et al., 1988, for example, used continuous delivery of bST in an oil based system at a dose of about 70 mg/d and showed a significant reduction in dressing percent. This might indicate that viscera and other non-carcass components have a broader bST dose-response window than components of the carcass. Concomitantly, the dose used by Wagner et al., 1988 was far in excess of that described as preferred herein. In a companion study Wagner et al., 1988, showed that a 960 mg dose administered about every two weeks produced about a 38-fold (3770% increase) in serum bST levels, when examined twelve days post injection of the second 960 mg dose. Such blood level changes in bST are in far excess of those required to stimulate carcass growth in steers, but potentially within the dose response of

tissues associated with the non-carcass component. Accordingly, a controlled release of bST within the window for increasing dressing percentage is preferred.

In Example 4 below, intraperitoneal bST osmotic implants in feedlot cattle increased dressing percent from 61.8% for the controls up to 62.4 to 62.8% for bST treated animals. Possible explanations for this effect included 1) presence of performance enhancers (e.g., an estrogenic agent) and 2) the mode of delivery (zero-order intraperitoneal delivery). In Example 3 below, the synergistic effect of an estrogenic agent and intraperitoneal zero-order delivery of bST is demonstrated. Neither product alone caused a significant increase in dressing percent, but in combination-treated cattle there was a significant increase in dressing percent.

In a study in which cattle received an estrogenic agent and intraperitoneal bST pellets, dressing percent was not significantly affected by treatment. However, as noted above, Wagner et al., 1988 had tested a combination of an estrogenic agent and bST delivered on a continuous basis, but had found that dressing percent still dropped from 63.0% to 61.4% which advances the unexpected advantage of the current invention. It is possible that Wagner et al.'s failure to demonstrate a bST/estrogen-induced improvement in dressing percent was due to 1) the excessive bST dose (70 mg/d) and/or 2) poorly controlled bST delivery (a 960 mg 28-day dairy product injected every 14 days). Thus, the enhancement of dressing percent with an estrogenic agent and intraperitoneal bST zero-order delivery can be considered due to factors including, 1) the synergistic effects of bST and the estrogenic agent, 2) the effect of substantially zero-order osmotic bST delivery and 3) the effect of intraperitoneal delivery compared to subcutaneous delivery of bST.

Most preferably, the implant is such as described in Appendix A attached hereto and incorporated by reference. Such implants may contain about 800 mg bST and release bST at a nominal rate of about 6 to 7 mg/d. Two or more implants can be used concurrently to achieve a desired rate of release, for example, about 10 mg/d to 12 mg/d.

According to the invention, the implant, preferably providing a substantially constant release, is implanted in the intraperitoneal cavity of the bovine being treated. Implanting in the intraperitoneal cavity facilitates recovery of the implant with the non-carcass components of the bovine following slaughter. In addition, in accordance with the invention, the combination of intraperitoneal implant and substantially constant release has been found advantageous in facilitating a significant increase in dressing percent and carcass weight in bST-treated cattle.

Implantation is preferably accomplished via the left paralumbar fossa since this has been found, as indicated above, to facilitate implantation. The left paralumbar fossa is a generally triangular area on the bovine between the hip bone and the last rib and below the loin area on the left side. Tissue and hide depth here is about 0.5 to 2.0", but trocars used for implantation are generally on the order of 1 to 5 inches. The insertion depth of the trocar needs to be greater than the actual thickness of the paralumbar region due to stretching of the peritoneal lining. The only internal organs presenting a risk of injury is the rumen. Damage to the rumen can be eliminated or reduced by administering the implant to fasting or feed restricted animals. See Appendix B attached hereto and incorporated by reference. Other methods of intraperitoneal administration may also be used.

According to the invention, bST is released intraperitoneally concurrently with administration of an effective dose of an estrogenic agent. The estrogenic agent can be administered either subcutaneously or intraperitoneally.

Any estrogenic substance may be used as the estrogenic agent in the present invention. An estrogenic substance is one which when administered to a normal female animal will cause growth of the uterus and teats. However, only estrogenic substances which are suitable for administration to food animals can be put into actual use.

In actual use, the acceptable estrogens for food-producing animals are estrone and estradiol steroids such as 17-beta estradiol, estradiol benzoate, ethinylestradiol, etc. or non-steroidal compounds with estrogenic activity, such as diethylstilbesterol, hexestrol, dianestrol, zeranol, etc., and derivatives of these substances. The simple esters, such as the C1-C6 alkanoates, and the benzoates, formed on one or two of the available hydroxy groups of estradiol and zeranol, or on the one hydroxy group of estrone are useful estrogenic substances. For example, estradiol benzoate, estradiol dipropionate, estrone acetate, zeranol hexanoate, zeranol dibutyrate, 17-beta-estradiol, 17-beta-ethinyl-estradiol, can be used.

Other components which do not interfere with the desired estrogen effect, such as progesterone, cholesterol, and other binding agents, and additives may also be present.

Broadly the estrogen can be released in the range of about 5ug/d to 500ug/d or even higher. Preferably the estrogen is released in the range of about 15 to about 60 ug/d. Generally, the dose of estrogenic agent can advantageously be the same as that used when the estrogenic agent is administered as an anabolic agent to

cattle in the finishing stage of growth to significantly increase body weight (BW) or carcass weight (CW). When the estrogenic agent is released from an intraperitoneal osmotic pump, the effective dose may be even lower, for example, in the range of 15 to 30 ug/d.

As indicated, the estrogenic agent is delivered concurrently with the intraperitoneal release of bST. The administration of the estrogenic agent can be by pellets or other means such as are well-known in the art. Preferably, the estrogenic agent is delivered intraperitoneally in the bovine using an osmotic pump, for example, the osmotic pump employed for the bST or another separate osmotic pump containing the estrogenic agent in a suitable excipient.

Preferably, the estrogenic agent is released in the bovine for a period of time generally concurrent with the period of bST delivery. However, treatment with an estrogenic agent prior to and concurrent with initial bST treatment has also been found effective.

Preferably the bST and/or estrogenic agent implant is implanted into the animals at the beginning of the finishing stage of growth. However, either the estrogenic source or the bST implant or both may also be implanted earlier and either provide a delayed initiation of bST release or a longer period of release.

In accordance with the invention, the intraperitoneal bST release is provided preferably during the entire period of the finishing stage of growth and is continued substantially until the time for slaughter of the animals. It has been previously found that the benefits of bST treatment may be adversely affected by discontinuation of bST. Hence, it is preferred that bST treatments continue at least until a time when the beneficial effects of concurrent bST and estrogen treatment will persist at slaughter, for

example, until about two weeks before slaughter and most preferably that bST release be ongoing at slaughter.

The period of time during which an effective rate of intraperitoneal release must be maintained can be any period effective for significantly increasing dressing percentage and carcass weight in finishing cattle receiving an estrogenic agent. Currently, it is believed that a minimum of about 6 or even about 9-12 weeks are required. The period of bST release is preferably at least for about 12 weeks prior to slaughter and more preferably about 18 or more weeks prior to slaughter. Overall, the period of bST treatment can be from about 6 to about 24 or 30 weeks or longer preceding slaughter of the beef cattle.

To obtain full benefit of the intraperitoneal release of bST, it is preferred that the bovines be on a supplemented diet, that is, on a diet that contains more protein or carbohydrate or fat or combinations of these than is found in hay or pasturage.

The invention will be further understood and appreciated from the following Examples.

Example 1 -- Weekly
Subcutaneously Administered Pellets

A study was undertaken to determine the effect of 40 or 80 mg A-bST pellets administered subcutaneously weekly during a 84-day beef cattle study on 1) growth, 2) feed efficiency and 3) carcass composition.

One hundred eighty Angus X Hereford beef steers weighing approximately 350 kg (770 lbs) were used. Stocking density was 5 animals per pen. The trial consisted of 180 steers with replicates of 12 pens (60 animals) per treatment group (control, 40 mg bST/wk, and 80 mg bST/wk). The study lasted 84 days (12 weeks) exclusive of the pretreatment period. The diet for all animals, on a dry matter basis, contained 16% crude

protein ("P"). Potable water was available ad libitum. Pens were randomly distributed among treatments:

Trial	Treatment Group	Pens	Animals	Description
1	1	12	60	Control
1	2	12	60	40 mg/wk A-bST Pellets
1	3	12	60	80 mg/wk A-bST Pellets

The animals were slaughtered for carcass analysis. The results are shown on the following Table:

TABLE

	TREATMENT		
Parameters	Control	40 mg/wk bST Pellets	80 mg/wk bST Pellets
Initial Body Wt (kg)	390.3	390.3	390.3
Final Body Wt (kg)	499.5[a]	495.0[a]	510.4[b]
Carcass Wt. (kg)	308.3	304.3	312.2
Dressing Percent (%)	61.7	61.5	61.2
Carcass Gain Response (%)	--	No Gain	39%
Non-Carcass Gain Response (%)	--	No Gain	61%

a, b - different superscripts indicate that numbers in a row are significantly different ($p<.05$).

It was observed that neither dressing percentage nor carcass weight were significantly increased. Further, at the higher dosage, it was observed that most of the increase in body weight due to bST treatment was allocated to the non-carcass components.

Example 2 -- Weekly Subcutaneous or Intraperitoneal Pellets

A study was undertaken to determine whether the effect of 80 mg A-bST pellets during an 84-day beef cattle study was comparable when administered subcutaneously and intraperitoneally.

Two hundred seventy Angus X Hereford beef steers weighing approximately 350 kg (770 lbs) were bought and

divided into three study groups. Stocking density was 5 animals per pen. Each study group consisted of replicates of 6 pens (30 animals) per treatment group (control, 40 mgbST/wk subcutaneous pellet, and 80 mgbST/wk intraperitoneal pellet). The study lasted 84 days exclusive of the pretreatment period. The diet for all animals, on a dry matter basis, contained 16% crude protein. Potable water was available ad libitum. Pens were randomly distributed among the treatments:

Trial	Treatment	Pens	Animals	Description
2	1	12	30	Control
2	2	12	30	80 mg/wk A-bST Subcutaneous (SQ) Pellet
2	3	12	30	80 mg/wk A-bST (IP) Intraperitoneal Pellet
3	1	12	30	Control
3	2	12	30	80 mg/wk bST SQ Pellet
3	3	12	30	80 mg/wk bST IP Pellet
4	1	12	30	Control
4	2	12	30	80 mg/wk A-bST SQ Pellet
4	3	12	30	80 mg/wk A-bST IP Pellet

The animals were slaughtered for carcass analysis. The results are shown in the following Tables:

TABLE

	TREATMENT		
Parameters	Control	80 mg/wk SQ bST Pellets	80 mg/wk IP bST Pellets
Initial Body Wt (kg)	395.1	395.0	397.7
Final Body Wt (kg)	493.7[a]	499.5[a]	507.8[b]
Carcass Wt. (kg)	304.2[a]	304.2[a]	311.2[b]
Dressing Percent (%)	61.6[a]	60.8[b]	61.2[ab]

Carcass Gain Response (%)	--	0%	61%
Non-Carcass Gain Response (%)	--	100%	39%
a, b - different superscripts indicate that numbers in a row are significantly different ($p<.05$).			

It can be seen that, while the dressing percentage of subcutaneously-treated cattle was significantly decreased relative to the control, the dressing percentage of intraperitoneally-treated cattle was not significantly changed relative to the control.

Example 3 - Combination of Intraperitoneal bST Osmotic Pump and Estrogen Pellets

A study was undertaken to determine the effects of intraperitoneal release of bST, of subcutaneous estrogen pellets, or of the combined effects of the two.

Two hundred fifty-six cross-bred large frame steers weighing approximately 430 kg (966lb) were assigned to a control group and three treatment groups and implanted with intraperitoneal bST pumps or/and subcutaneous estrogen pellets. The bST formulation used was a 35% Zn^{-} bST load in a phosphate buffer, glycerol, and Tween-80. The w/w/w% proportions respectively were 48.38/48.38/0.24. The phosphate buffer was 60:40 monobasic:dibasic sodium phosphate at 1.0M. The time of release of both bST and estrogen was 87 days prior to slaughter. The results are shown in the following Table.

TABLE

Parameters	TREATMENT					
	Control	12mg/d bST O Estrogen	O bST/200ug/d Estrogen	12mg/d bST//200ug/d Estrogen		
Initial Body Wt (kg)	430.3	430.3	430.3	430.3		
Final Body Wt (kg)	544.9[a]	552.2[b]	567.1[c]	576.4[d]		
Carcass Wt (kg)	334.2[a]	340.3[b]	349.3[c]	359.7[d]		
Dressing Percent (%)	61.3[a]	61.6[a]	61.6[a]	62.4[b]		
Carcass Gain Response (%)	N/A	84%	68%	112%		
Non-Carcass Gain Response (%)	N/A	16%	32%	-12%		

These results indicated that a significant improvement in dressing percentage and carcass weight were achieved by intraperitoneal osmotic pump release of bST concurrent with estrogen treatment.

Example 4 - Combination of Intraperitoneal bST Osmotic Pump and Estrogen Pellet

A study was undertaken to determine performance of intraperitoneal osmotic pumps in finishing cattle concurrently being administered estrogen. Six hundred seventy-two cross-bred large frame cattle weighing

approximately 412 kg were bought and assigned to a control group and six treatment groups of 96 cattle each. The cattle were implanted with intraperitoneal osmotic pumps capable of delivering 6, 12, 15 or 18 mg bST per day during an 84-day period ending with slaughter. The cattle received subcutaneous estrogen pellets during a 126-day period ending with slaughter. The estrogen release is estimated at about 200 ug/d. The results are shown in the following table.

TABLE

	TREATMENT							
		30% bST Load		40% bST Load	45% bST Load			
Parameters	Control	6mg/d	12mg/d	15mg/d	6mg/d	12mg/d	18mg/d
Initial Body Wt (kg)	411.9	411.9	411.9	411.9	411.9	411.9	411.9
Final Body Wt (kg)	555.1[a]	565.6[bc]	568.7[bc]	569.6[c]	561.8[b]	563.5[bc]	566.5[bc]
Carcass Wt (kg)	343.0[a]	353.1[bc]	357.2[d]	355.4[cd]	350.8[b]	351.3[b]	353.8[bc]
Dressing Percent (%)	61.8[a]	62.4[b]	62.8[b]	62.4[b]	62.4[b]	62.4[b]	62.5[b]
Carcass Response (%)	--	96%	104%	86%	116%	99%	95%
Non-Carcass Response (%)	--	4%	-9%	14%	-16%	1%	5%

The results of Examples 3 and 4 indicate that concurrent intraperitoneal treatment of finishing beef cattle with intraperitoneal bST and estradiol significantly increase dressing percentage and carcass weight and furthermore allocate most of the increased weight to the carcass components.

CLAIMS

1. A method of preparing beef cattle for slaughter comprising:

inserting into the intraperitoneal cavity of a bovine in the finishing stage of growth a source of bovine somatotropin effective for prolonged release;

the bovine being administered an estrogenic substance at a rate effective for increasing one of average daily gain and carcass weight and body weight of cattle;

the source of somatotropin releasing intraperitoneally in the bovine a dose of bovine somatotropin sustained in a range effective for increasing average daily gain of cattle;

continuing the somatotropin release in the bovine for a period of time greater than about 9 weeks and continuing substantially until slaughter of the bovine;

the bovine maintaining an average daily gain greater than 1 kilogram per day during said period.

2. The method of Claim 1 wherein:

the source of somatotropin is effective for approximately zero order delivery of a dose of bovine somatotropin in the range of about 3 to about 14 milligrams per day.

3. The method of Claim 1 wherein:

the source of somatotropin is effective for approximately zero order delivery of a dose of bovine somatotropin in the range of about 6 to about 14 milligrams per day.

4. The method of Claim 1 wherein:

the source of somatotropin is effective for approximately zero order delivery of a dose of bovine somatotropin in the range of about 9 to about 14 milligrams per day.

5. The method of Claim 1 wherein:
the period of somatotropin release is continued for a period greater than about 12 weeks and continuing substantially until slaughter of the bovine.

6. The method of Claim 1 wherein:
the period of somatotropin release is continued for a period greater than about 18 weeks and continuing substantially until slaughter of the bovine.

7. The method of claim 1 wherein
the period of somatotropin release is continued for a period from about 12 weeks to about 30 weeks ending substantially with slaughter of the bovine.

8. The method of Claim 1 wherein:
the source of somatotropin is effective for substantially zero order intraperitoneal release during a prolonged period of time.

9. The method of Claim 1 wherein:
the bovine is administered an estrogenic substance at a dosage in the range of about 5 to about 500 micrograms per day.

10. The method Claim 1 wherein:
the period of time comprises a period when the average weight of the cattle is equal to or greater than about 320 kg (700 pounds).

11. The method of Claim 1 wherein:

the period of time comprises a period when the cattle are experiencing an average daily gain equal to or greater than 1.5 kilograms per day.

12. The method of Claim 1 wherein:

the period of time commences at the time of transfer of a bovine to a feedlot and continues until slaughter.

13. The method of Claim 1 wherein:

the source of bovine somatotropin further comprises the estrogenic agent.

14. A method of preparing beef cattle for slaughter comprising:

inserting into the peritoneal space of cattle in the finishing stage of growth a source of bovine somatotropin effective for prolonged release;

the cattle further being treated with an estrogenic agent at a dose effective for increasing the body weight or carcass weight or both of bovines;

releasing bovine somatotropin in the intraperitoneal space at a dose effective for increasing a parameter selected from the group consisting of body weight, carcass weight, feed conversion efficiency or average daily gain of bovines; and

the bovine somatotropin and the estrogenic agent being effective for significantly increasing the dressing percentage and carcass weight of bovines relative to non-bovine-somatotropin- non-estradiol-treated cattle.

WHAT IS CLAIMED:

1. A method of implanting large diameter objects in the intraperitoneal cavity of bovines which can be accomplished readily, without significant injury to the bovine, requires minimal care after implantation, and rapidly heals, comprising:

providing a generally cylindrical large diameter object having an outside diameter in the range of about 8 to about 15 millimeters (mm);

making an incision of less than about 25mm in length in the hide of the left paralumbar fossa of a bovine, the incision having an orientation and length and depth such that gaping of the resulting wound substantially does not occur after inserting the object therethrough;

inserting a generally cylindrical tube having an external diameter of less than about 25mm for passing through the opening and having an internal diameter for passing the large diameter object therethrough and having a non-hide-incising tip effective for penetrating tissues underlying the incision and for puncturing the peritoneum and having a length for extending through the incision, underlying tissues, and into the peritoneal cavity of the bovine;

causing the tip to penetrate the underlying tissues and to puncture the peritoneum and inserting the large diameter object therethrough; and

removing the tube.

2. The method of Claim 1 wherein:

the incision comprises a vertical incision.

3. The method of Claim 1 wherein:

the inserting step is conducted at a time when the rumen is not distended significantly into a portion of the peritoneal cavity being targeted.

4. The method of Claim 1 wherein:
the bovine is a bovine fasting or feed-restricted for 6 to 24 hours prior to implantation.

5. The method of Claim 1 wherein:
the bovine is a bovine fasting or feed-restricted for 10 to 18 hours prior to implantation.

6. The method of Claim 1 wherein:
the opening of the hide is less than about 20mm.

7. The method of Claim 1 wherein:
the object is an osmotic pump capable of delivering about 3 to about 14 mg/day of bovine somatotropin for a period of greater than 9 weeks and optionally containing an estrogenic agent.

8. The method of Claim 1 wherein:
the tube and its contents are sterilely packaged with the large diameter objects therein and sterility is maintained until immediately prior to the inserting step.

9. The method of Claim 1 wherein:
the sterility of an outside portion of the tube which will extend from hide to peritoneal cavity is maintained by a sheath removable prior to use.

10. The method of Claim 1 wherein:
the incision is substantially through the hide only.

11. A device for the intraperitoneal or subcutaneous implantation of large diameter size-invariant objects into a bovine, comprising:

a tube of moldable plastic having an outside diameter of less than about 25mm and an inside diameter in the range of about 8 to about 15 mm in a first portion of its length which will extend from hide to intraperitoneal cavity adjacent the left paralumbar fossa in a bovine,

a first end of the tube having a non-hide-incising tip effective for penetrating tissues underlying an incision in the hide and for puncturing the peritoneum, the tube having adjacent the first end thereof means for releasably retaining the large diameter objects in the tube while the tube is inserted into an incision in the bovine's hide and having adjacent a second end thereof a slidable seal for sealing the second end and for urging large diameter objects within the tube past the releasing means and out of the first end of the tube.

12. The device of Claim 11 wherein:

the tube comprises a first body portion adjacent the first end and a second body portion adjacent the second end, the first body portion having a length effective for extending through the incision, underlying tissues, and into the peritoneal cavity of the bovine;

the retaining means being a constriction which can flex outwardly integrally molded adjacent the first end in an interior portion of the plastic tube; and comprising

a sheath covering and maintaining sterile the first body portion and causing the large diameter objects not to rest against the retaining means while the sheath covers the first body portion.

13. The device of Claim 12 wherein:

the constriction integrally molded in the plastic tube comprises a protuberance on an internal surface of the tube adjacent the first end on the

side of the tube having the greatest length, the protuberance being adapted to flex and permit the large diameter objects to pass thereby.

14. The device of Claim 13 wherein:

the protuberance is adapted to flex by its location on a flexible strip integrally molded with the tube and not interrupting the perimeter of the first end.

15. The device of Claim 14 wherein:

the seal comprises a molded elastomer plug having a recess therein for receiving a rod which can be used to urge the seal through the first and second portions of the tube.

16. The device of Claim 12 wherein:

the seal further comprises first and second sidewall-engaging portions for slidably and sealingly engaging the sidewall of the tube compensating for taper and irregularities of the tube.

17. The device of Claim 16 wherein:

the seal comprises an axial extension directed toward the first end of the tube having a length for ensuring that the large diameter objects can be moved towards the first end and out of engagement with the restraining means.

18. The device of Claim 12 wherein:

the combined length of the first and second body portions are sufficient for enclosing a number of large diameter objects being administered in a single administration.

19. The device of Claim 12 wherein:

the first body portion has a lesser outside diameter than the second body portion forming a

shoulder therebetween demarcating a desired depth of insertion for penetrating the peritoneum.

20. The device of Claim 12 wherein:

the sheath is adapted for maintaining sterility of the first body portion until removal.

21. An article of manufacture comprising:

a plastic tube having a non-hide-incising tip at a first end, the tip being effective for penetrating bovine tissues underlying an incision in the hide and being effective for penetrating the intraperitoneal cavity of the bovine;

a plastic sheath sterilely enclosing a first portion of the tube adjacent the first end, the first portion having a length effective for extending from left paralumbar fossa of a bovine into the intraperitoneal cavity;

retaining means adjacent the first end for releasably retaining objects within the tube after the sheath is removed;

the objects within the tube being one or more osmotically-driven pumps having an outside diameter of about 8 to about 15mm for delivery of a beneficial agent; and

a seal adjacent the second end of the tube for completing sterile or low bioburden enclosure of contents of the tube.

22. The article of Claim 12 wherein:

the tube contains one or more osmotic pumps for delivering bovine somatotropin intraperitoneally in a bovine;

the osmotic pump being sterile and sterilely packaged in said tube and having a sheath thereon for maintaining a first exterior portion of the tube

sterile and having the seal therein completing sterile enclosure of the osmotic pump.

23. The article of Claim 22 wherein:
the tube, the sheath, and the seal are further substantially impermeable to moisture.

24. The article of Claim 21 wherein:
the article is sterilely sealed in a moisture impermeable covering prior to use.

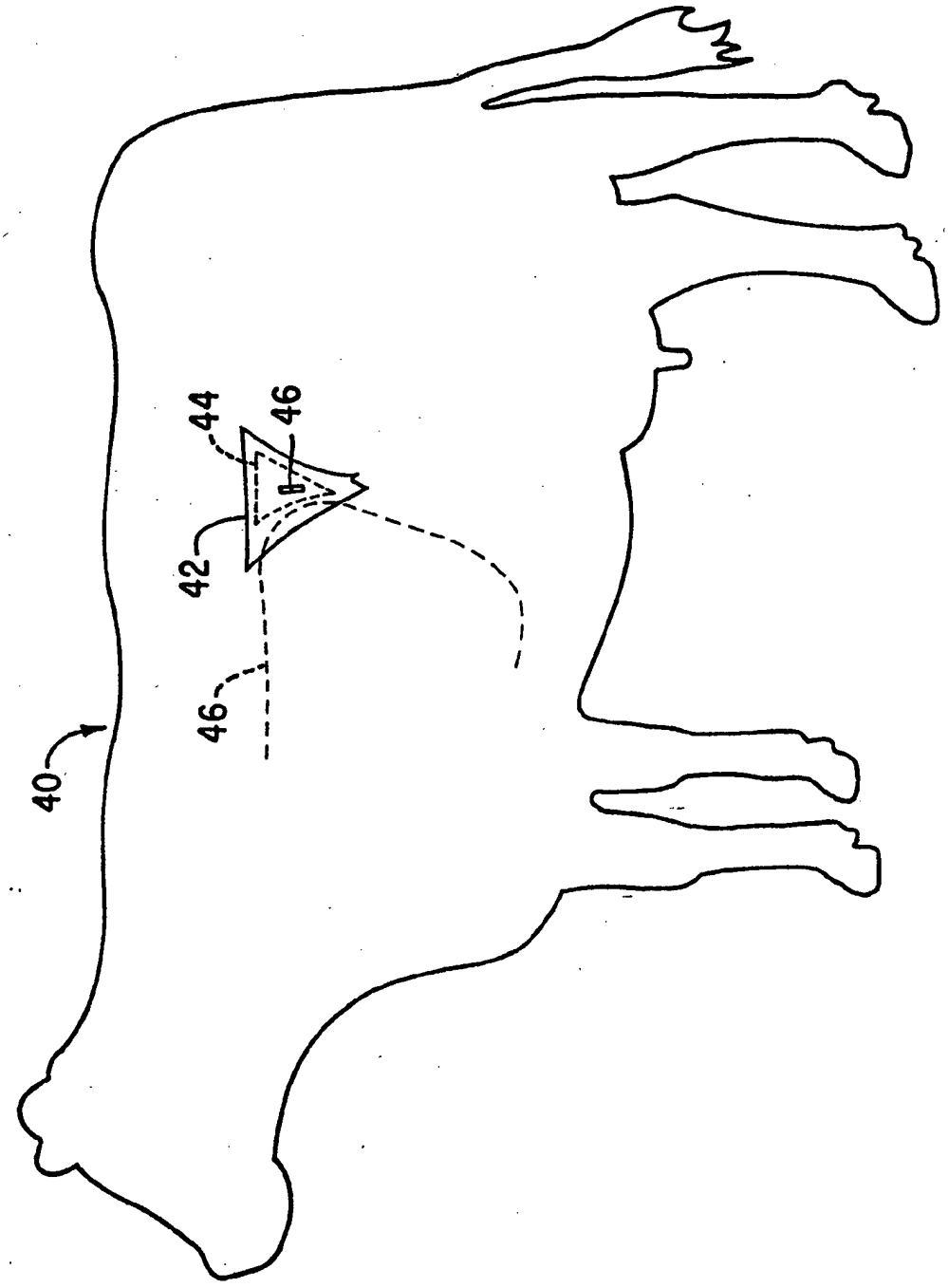

FIG. 1

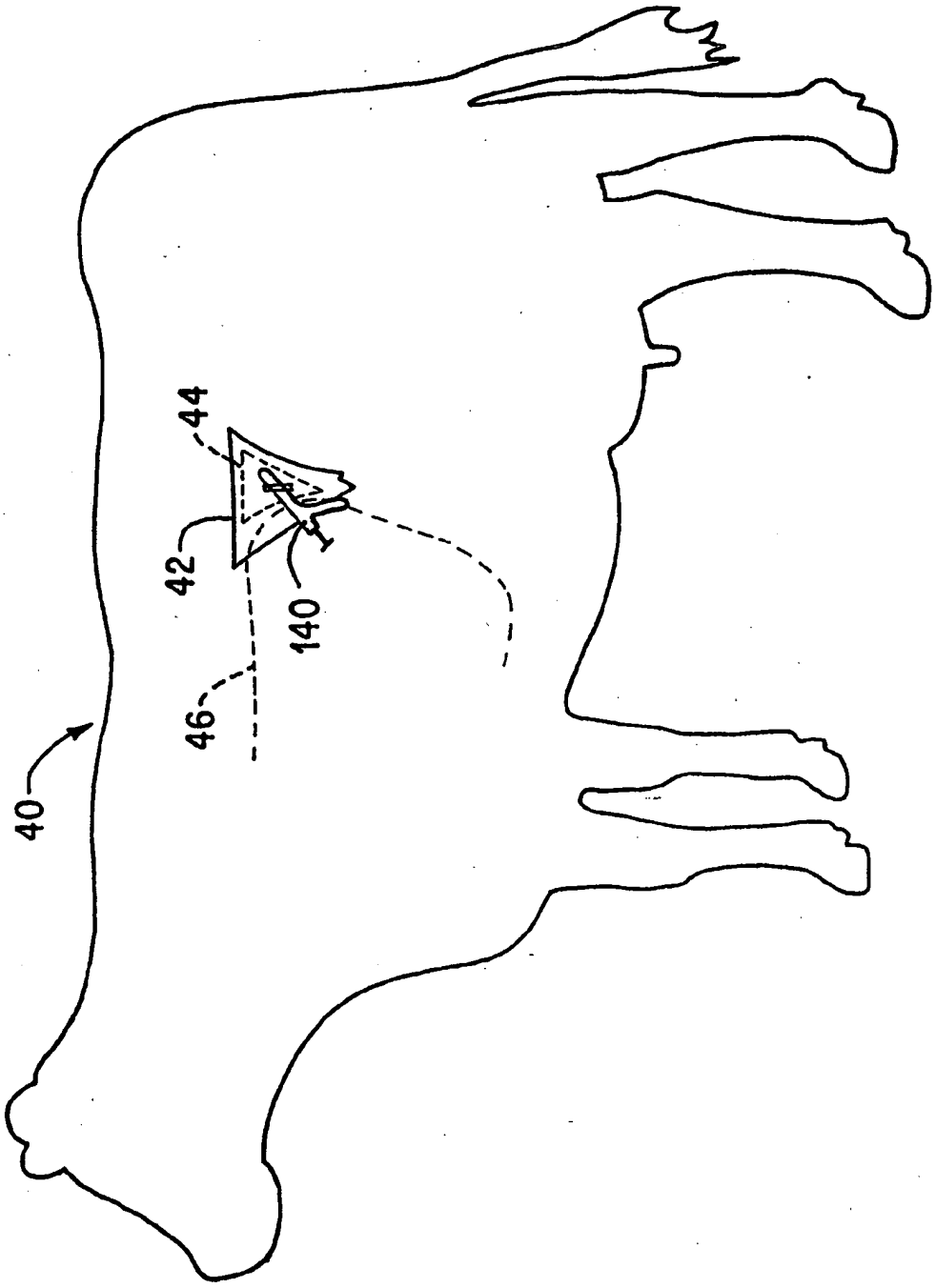

FIG. 2

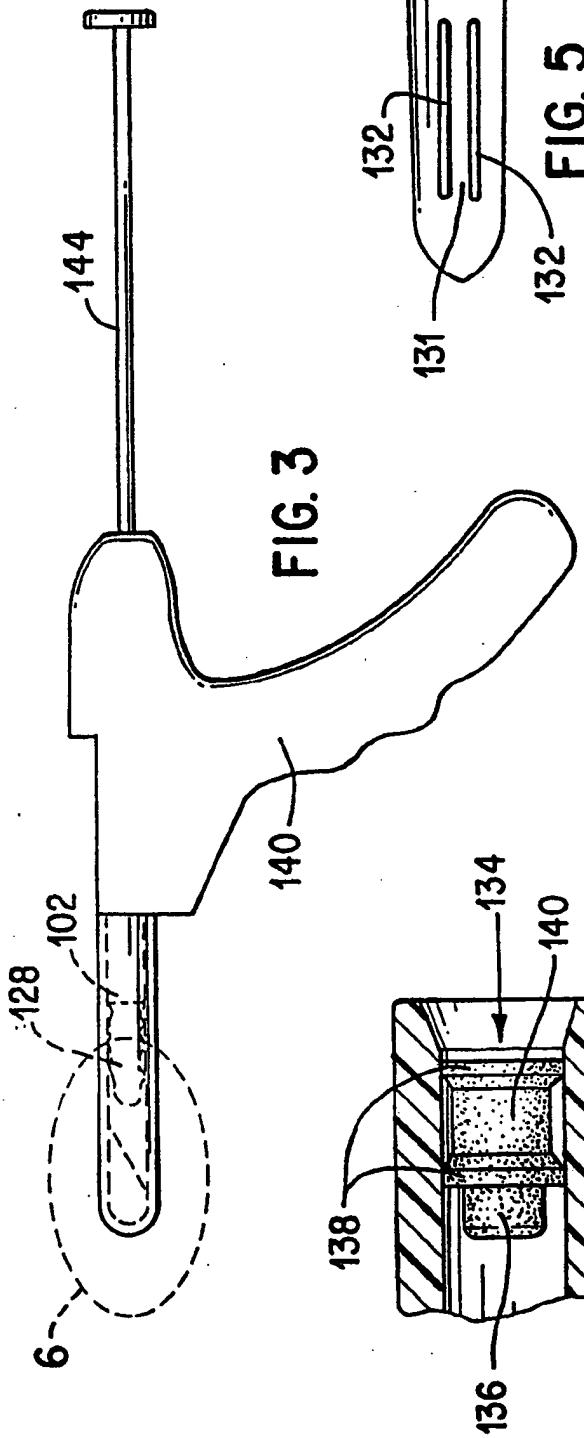

FIG. 3

FIG. 5

FIG. 4A

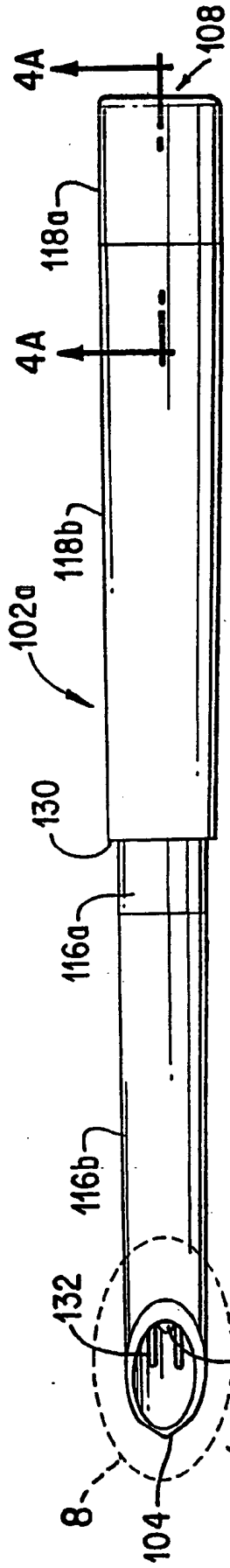

FIG. 4

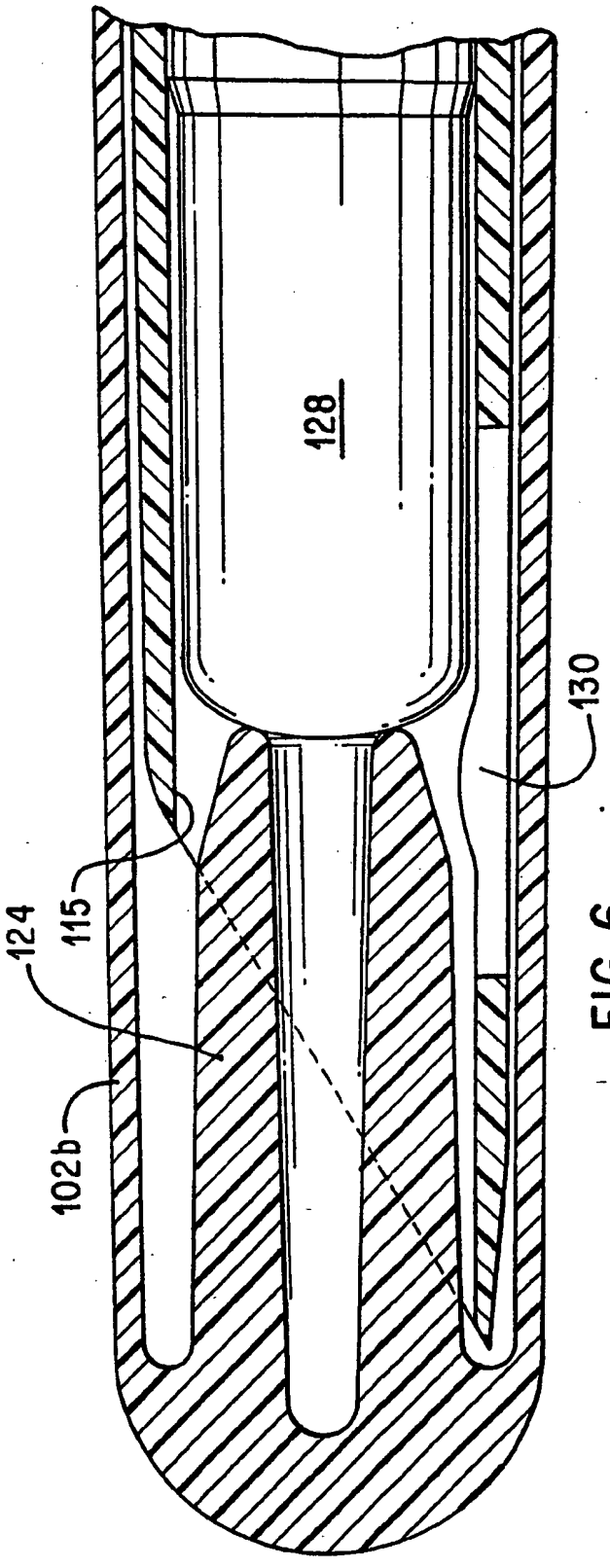

FIG. 6

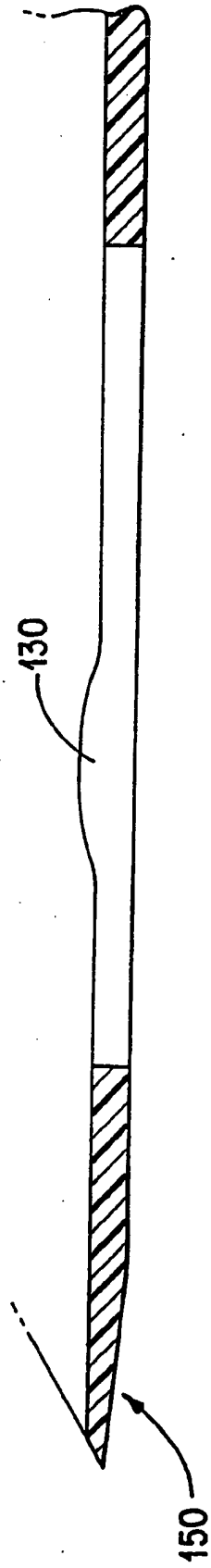

FIG. 7

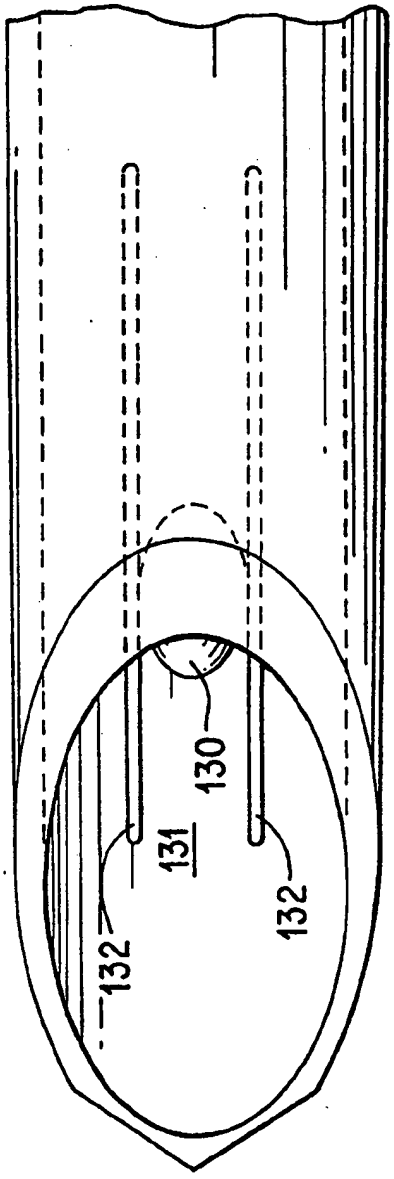

FIG. 8

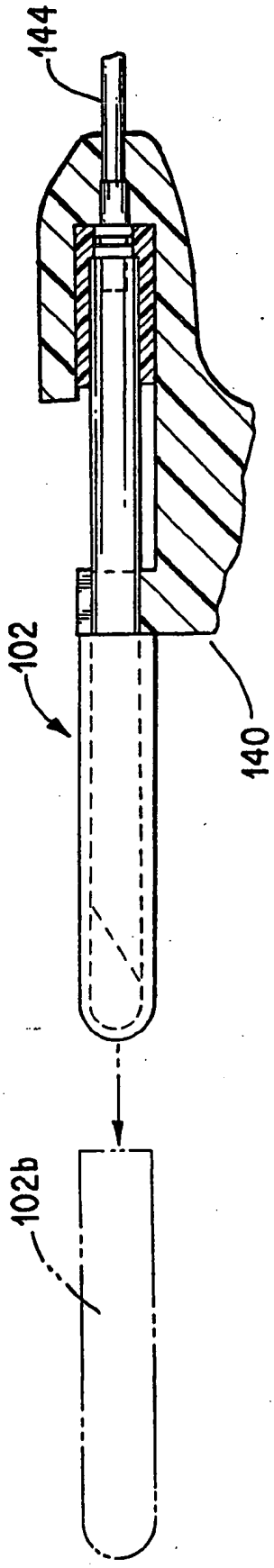

FIG. 9

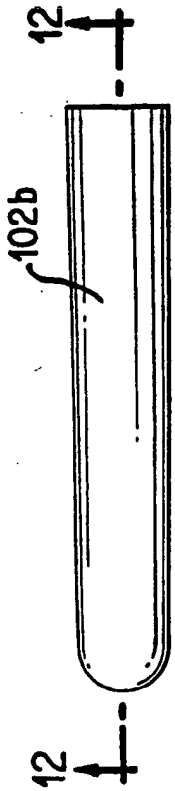

FIG. 11

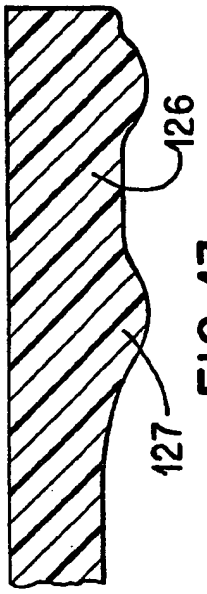

FIG. 13

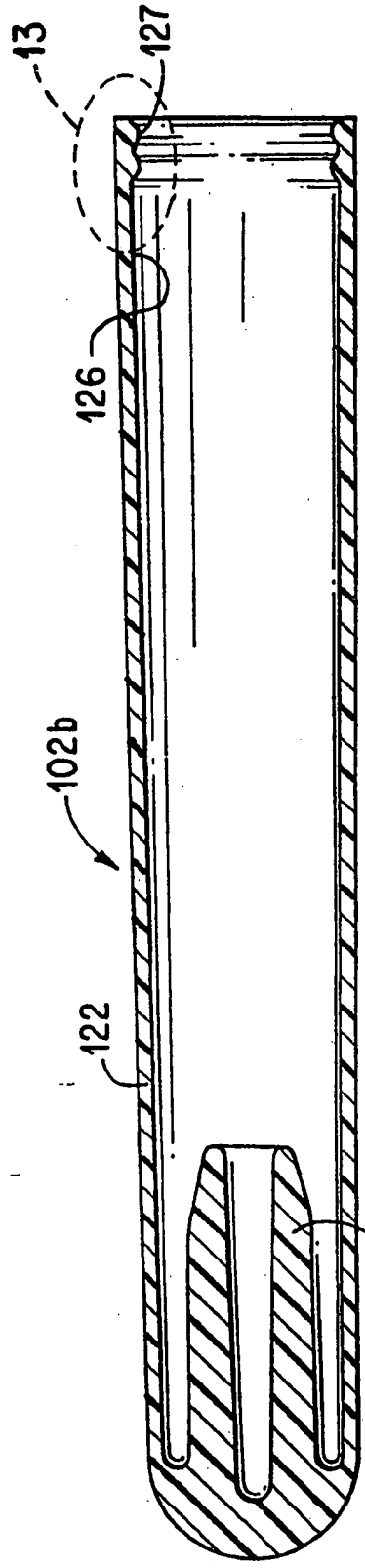

FIG. 12

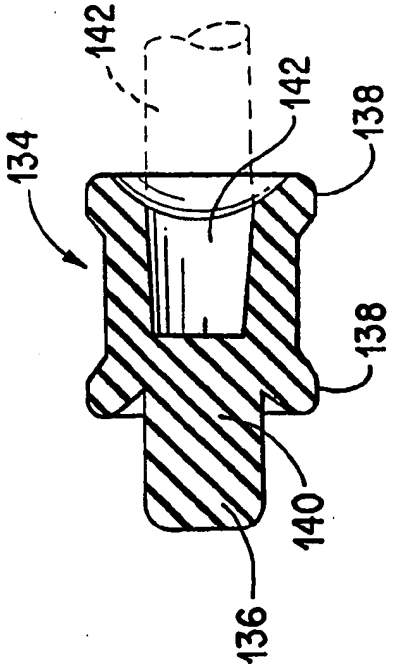

FIG. 10

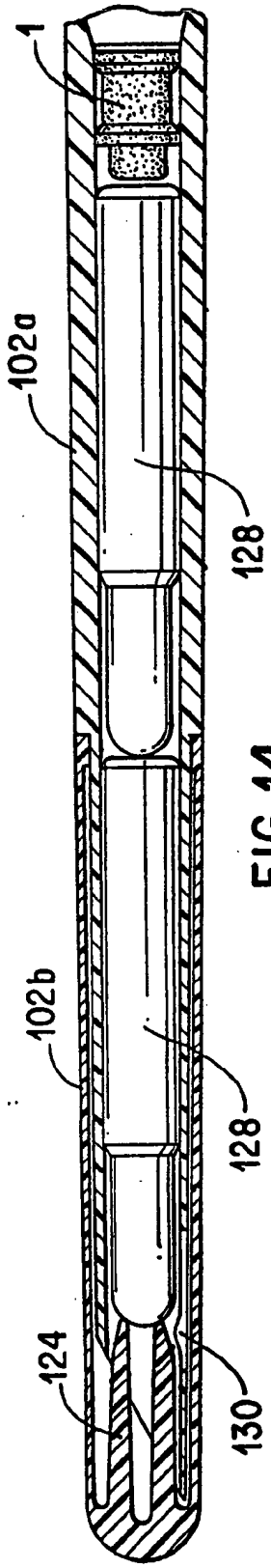

FIG. 14

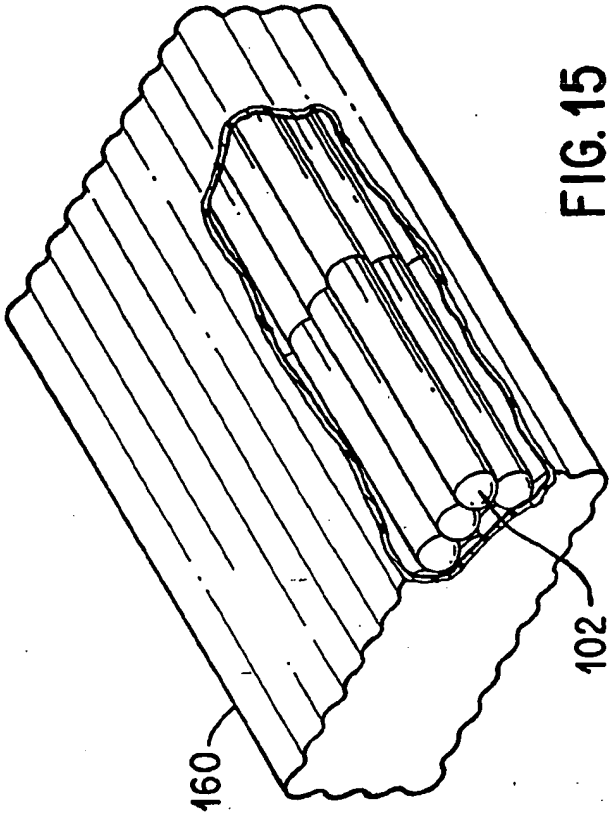

FIG. 15

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 95/08330

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/22 A61D7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 16194 (ALZA CORPORATION) 1 October 1992 see the whole document see page 17, line 13 - line 17	1-31
A	US,A,5 137 727 (ECKENHOFF) 11 August 1992 see the whole document see figure 2	1-31
A	EP,A,0 373 867 (ALZA CORPORATION) 20 June 1990 cited in the application see the whole document see figure 8	1-31
A	EP,A,0 374 120 (MONSANTO COMPANY) 20 June 1990 see page 4, line 26 - page 8, line 20	1-31

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 1995	12. 12. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Benz, K

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH RE..

Information on patent family members

Inte. .onal Application No
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